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STUDIES IN EXPERIMENTAL HYPERTENSION[1, 2]

I. Phenol Red Excretion and Renal Blood Flow in Hypertension of Renal Origin

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The arterial hypertension produced in animals by partial occlusion of the renal arteries has been ascribed to renal ischemia. Goldblatt and his co-workers (1) demonstrated, in acute experiments, that varying degrees of compression of the renal artery produced immediate corresponding diminutions in the outflow of renal vein blood. Levy, Light and Blalock (3) measured the renal blood flow in dogs before and after the production of this type of hypertension and reported that the blood flow was regularly reduced during the period of elevated blood pressure. The method which they employed is suitable only for a few measurements in each animal, and the observations were not continued over a long enough period to determine whether the renal blood flow might return to normal in the course of several months or years, in spite of the persistence of hypertension. It is well recognized that in some dogs with hypertension, produced by partial obstruction of the renal arteries, an extensive collateral circulation to the kidney develops. To what extent this circulation is capable of restoring the renal blood flow to normal, and whether the persistence of hypertension is associated with permanent renal ischemia remains to be determined.

[1] Supported by a grant from the Commonwealth Fund for the Study of Essential Hypertension.

[2] This is the first of a series of papers which describe experiments undertaken as part of an integrated study of clinical and experimental hypertension. They deal with measurements of certain functions, including the blood flow, in the kidneys of dogs which were made hypertensive either after partial obstruction of main renal arteries by the method of Goldblatt, Lynch, Hanzal and Summerville (1) or by section of the moderator nerves by the method of Heymans (2). The data are presented in the chronological sequence in which they were obtained. The authors are deeply indebted to Dr. James Bordley III for his constant encouragement and help during the course of this work.

The experiments reported in this paper were originally undertaken to compare the urinary excretion of phenol red (phenolsulphonephthalein) in dogs with hypertension of renal origin with that of patients having essential hypertension. They were later extended to include studies of renal blood flow in these dogs. The results indicated that in the period of chronic hypertension the dogs' renal blood flow, as estimated from the phenol red excretion, was at the normal (prehypertensive) level.

METHODS

Five young female dogs weighing 10 to 13 kgm. were used. In four the left kidneys were explanted, with the renal veins isolated beneath the skin to make them readily accessible for venipuncture. Subsequently the right kidney was removed. In the fifth animal, the right kidney was explanted, and the left removed. In four of the animals the explant was carried out according to the method of Gordon, Alving, Kretzschmar and Alpert (4), while in one animal the technique of Sheehan (5) was used. The first of these methods was preferred because the isolation of the renal vein was found to be simpler and just as satisfactory. Samples of renal vein blood could be obtained quickly and repeatedly. Possible contamination of the renal vein blood by arterial blood, or urine from the kidney pelvis or ureter, was always kept in mind, but in more than 700 samples, the phenol red concentration in the venous blood was always less than that in the arterial blood. Arterial blood samples were obtained by femoral puncture.

Hypertension was induced in each dog by applying a Goldblatt clamp (1) to the renal artery of the explanted kidney *via* a transperitoneal approach, under light ether anesthesia.

The blood pressure was measured in the femoral artery 1 to 6 times weekly either by the Erlanger cuff method, as described by Wood and Cash (6), or by the Hamilton optical manometer (7). No significant discrepancies between the results obtained by the two methods were noted either in the daily records or when determinations were made simultaneously by both methods.

All studies of phenol red excretion and renal blood flow were carried out after a fast of 16 hours. The animals were trained to lie quietly on the table for the 60 minute period of each experiment. No anesthesia was used. Thirty minutes before the injection of the dye, 200 to 250 cc. of water were given by stomach tube, in order to maintain an adequate urine flow. An inlying catheter was placed in the bladder, and was washed out before the experiment was started. A 6 per cent solution of phenol red was injected into a leg vein, the total quantity amounting to 24 mgm. per kgm. of body weight. After determination of the appearance time, the excreted phenol red was collected at 5 minute intervals by washing the bladder with tap water at 38°C. The washing was begun 1¼ minutes before the end of each 5 minute period, and was concluded precisely at the end of the period. The collection of the blood samples was timed to begin about 20 minutes after the peak

of the excretion of the dye. At least three samples were taken, at 5 minute intervals, between the urine collections, from both the renal vein and the femoral artery in quick succession, the venous sample being drawn first. The exact time of withdrawal of each sample was noted to permit accurate interpolation. Potassium oxalate was the anticoagulant used. Portions of arterial blood were centrifuged in Wintrobe hematocrit tubes to determine the volume of plasma per cc. of blood.

TABLE I

Data for Typical Experiment with Calculations of Renal Blood Flow

Dog #19. Weight 12.5 kg. At beginning of experiment 300 mg. phenol red were injected into a leg vein.

URINARY PHENOL RED			PLASMA PHENOL RED				RENAL BLOOD FLOW CALCULATIONS TIMED FOR RENAL VEIN PUNCTURE
Time after injection	Total 5 min.	Mg. per min.	Arterial		Renal vein		
			Time	Mg. per cc.	Time	Mg. per cc.	
minutes	*mg.*						
20	16.12	3.22					
25	12.98	2.59					
26		[2.52]†		[0.0432]	26′00″	0.0227	$\frac{2.52}{.0432 - .0227} \times \frac{1.0}{0.55^*} = 222$
27			27′30″	0.0418			cc. per min.
30	11.17	2.23					
31		[2.20]		[0.0366]	31′00″	0.0181	$\frac{2.20}{.0366 - .0181} \times \frac{1.0}{0.55^*} = 217$
32			32′15″	0.0353			cc. per min.
35	10.36	2.07					
36		[2.02]		[0.0318]	35′45″	0.0168	$\frac{2.02}{.0318 - .0168} \times \frac{1.0}{0.55^*} = 245$
37			37′00″	0.0308			cc. per min.
40	9.17	1.83					

* Volume of plasma per cc. of blood.

† Brackets enclose urinary and arterial phenol red figures obtained by interpolation for time of drawing renal vein blood.

For estimation of the phenol red in the urine, each sample was alkalinized and diluted so that 1 cc. contained approximately 0.01 mgm. of the dye. The concentration was determined colorimetrically against a standard solution containing 0.01 mgm. of the dye per cc. Excretion curves were calculated in terms of per cent of the amount of total dye injected.

All plasma phenol red determinations were made after alcoholic extraction of the dye. Sheehan's method was slightly modified: 1 cc. of plasma was added

drop by drop to 10 cc. of absolute alcohol. This was shaken vigorously and allowed to stand for 20 hours. After centrifugation, the supernatant fluid was decanted. To complete the precipitation of protein, 1 cc. of a saturated solution of lead acetate in absolute alcohol was added to the supernatant fluid. After 2 hours, the precipitate was removed by centrifuging, and the supernatant fluid decanted and alkalinized by the addition of 1 drop of 1/10 N NaOH. All containers throughout the procedure were kept tightly stoppered. Any precipitate which appeared after the addition of alkali was allowed to settle. The clear solutions were transferred to narrow colorimeter cups (a narrow cup was used to minimize evaporation) and the dye concentrations were read against the standard alcoholic solutions of phenol red. The range of accuracy of this method, when known amounts of phenol red were added to plasma, was ±5 per cent.

The total renal blood flow was calculated from the equation:

$$F = \frac{E}{A - R} \times \frac{1.0}{\text{volume of plasma per cc. of blood}}$$

where F = Renal blood flow in cc. per minute.
E = Mgm. of phenol red excreted per minute.
A = Arterial plasma concentration of dye in mgm. per cc.
R = Renal vein plasma concentration of dye in mgm. per cc.

Table I shows the data and calculations of a typical experiment. It will be noted that the figures for arterial blood and urine were obtained by interpolation. The delay in the passage of the dye from blood stream to bladder was disregarded in the calculation. The reasons for not correcting for this factor will be discussed later. The three or more renal blood flow determinations in each experiment usually agreed within 15 per cent.

RESULTS

Constriction of the renal artery of the explanted kidney of these dogs subsequently produced an elevation in blood pressure of at least 65 mm. Hg systolic and 60 mm. Hg diastolic. In four dogs there was an interval of one to two weeks with normal or slightly elevated blood pressure before the appearance of severe hypertension. Such a lag period has been previously described by Goldblatt (1) in dogs which developed the benign form of hypertension. In only one animal, No. 19, was the clamp tightened after the original application.

Two dogs died in uremia, one and five weeks, respectively, after constriction of the renal artery. The first one was found to have developed thrombosis of the artery beneath the clamp. No arterial obstruction was noted in the second animal, which had a clinical course similar to the

"acute malignant phase" described by Goldblatt (1). The three remaining dogs were killed, 3, 7 and 11 months, respectively, after constriction of the renal artery, having maintained throughout that period

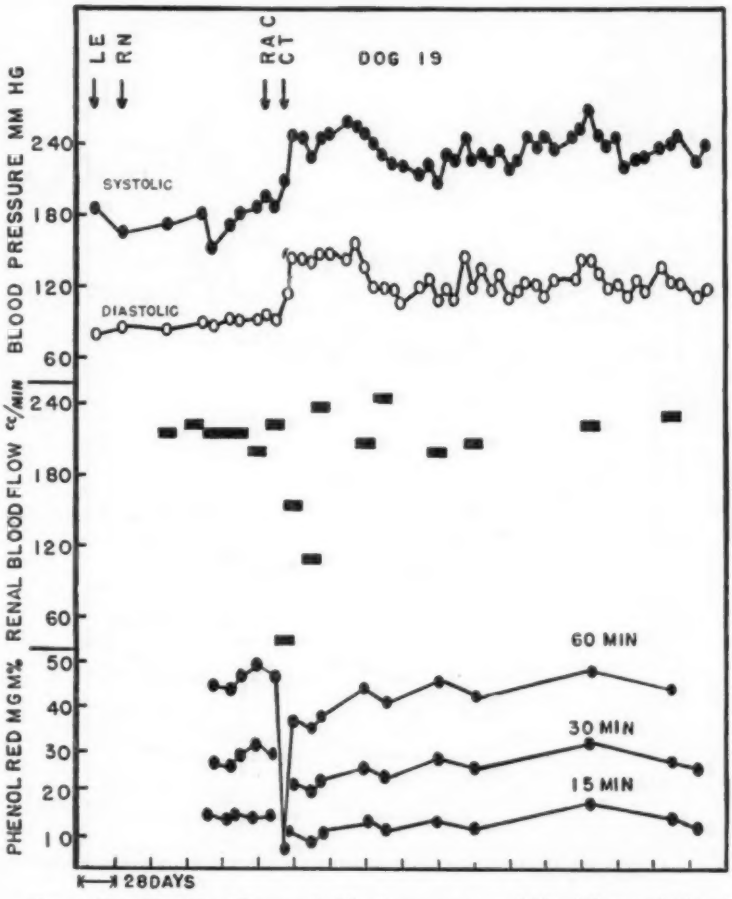

FIG. 1. Dog No. 19. Changes in blood pressure, renal blood flow and phenol red excretion before and after partial constriction of the renal artery. LE = left kidney explanted. RN = right nephrectomy. RAC = renal artery clamp applied to explanted left kidney. CT = clamp tightened.

an elevation of arterial pressure of at least 35 mm. of Hg systolic and 25 mm. Hg diastolic above the preoperative level (Figs. 1–3). None of these animals showed any rise in blood non-protein nitrogen. Although

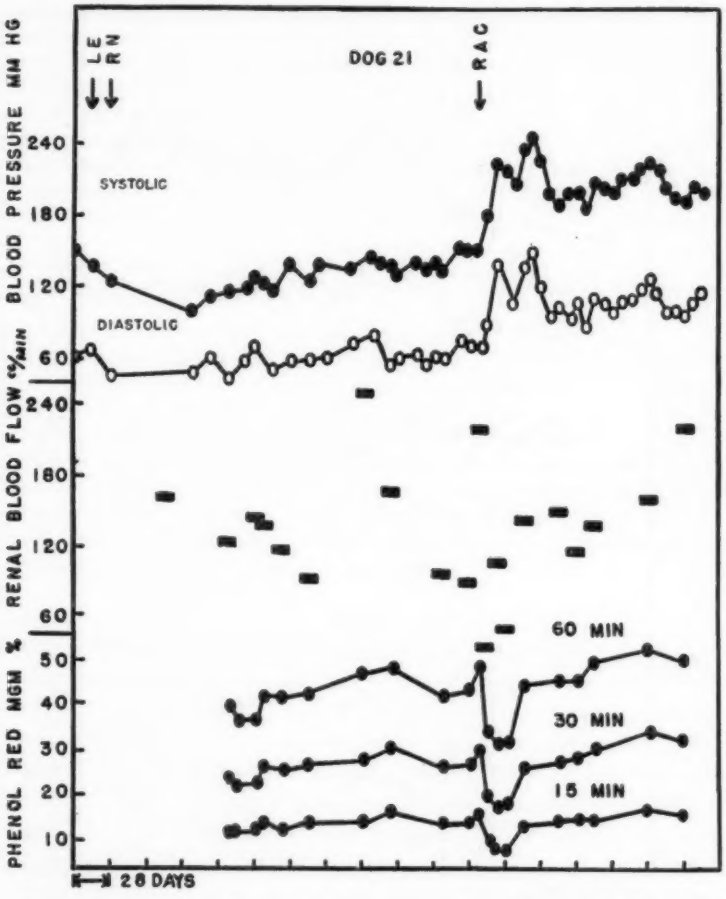

FIG. 2. Dog No. 21. Changes in blood pressure, renal blood flow and phenol red excretion before and after partial constriction of the renal artery. LE = Left kidney explanted. RN = right nephrectomy. RAC = renal artery clamp applied to explanted left kidney.

some of the dogs showed occasional traces of albumin in the urine throughout the study, no increase in albuminuria was noted during the period of hypertension.

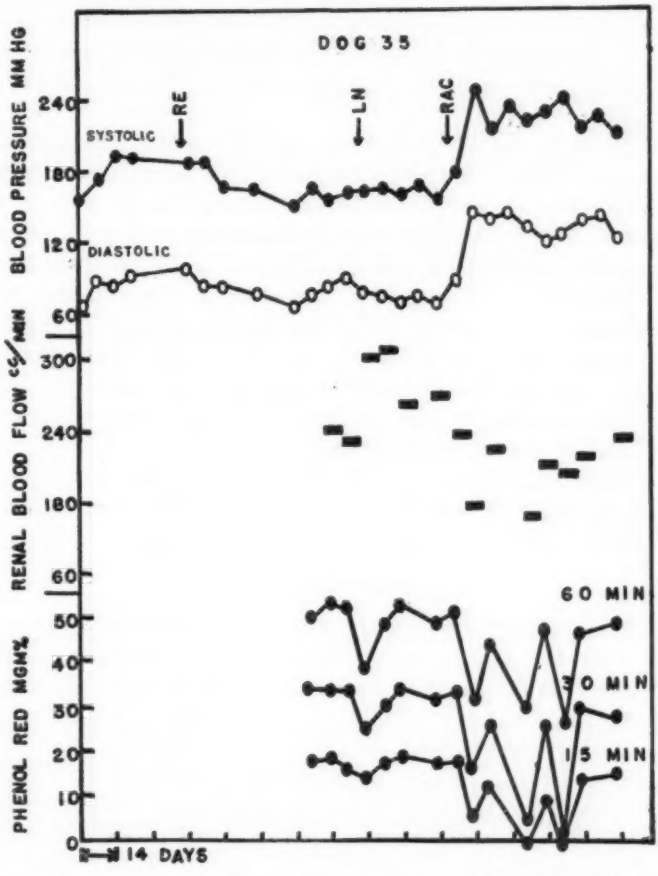

FIG. 3. Dog No. 35. Changes in blood pressure, renal blood flow and phenol red excretion before and after partial constriction of the renal artery. RE = right kidney explanted. LN = left nephrectomy. RAC = renal artery clamp applied to explanted right kidney.

Excretion of Phenol Red

During the prehypertensive periods, the excretion of phenol red in the urine was constant in repeated experiments on the same animal. The total phenol red excretion was decreased after removal of the unexplanted kidney, but recovery occurred gradually until, at the end of 1½ to 8 months, depending on the animal, the remaining kidney was excreting the dye at a rate approximately equal to that originally observed in both kidneys.

Following the application of the clamps, the excretion of phenol red was unchanged during the prehypertensive period, except for one dog, in which a marked decrease was found on the day before the blood pressure began to rise. In the other dogs, simultaneously with, or shortly after the onset of hypertension, a marked reduction in output of the dye was uniformly noted. This was most marked for the first 15 minute period after injection. It was also found that the peak of excretion of the dye was delayed until 5 to 15 minutes later than in the pre-hypertensive period. The reduction in excretion persisted to a variable degree for 4 to 7 weeks following the onset of elevated blood pressure. At the end of that time, in the three animals that were observed for long periods, a rapid or gradual increase in excretion took place until the control level was finally reached. Moderate hypertension peristed throughout this period, but the blood pressure fell slightly after 6 to 8 weeks.

Renal Blood Flow

There were daily fluctuations in the total renal blood flow of the normal dogs, as has been noted by other investigators, and the degree of fluctuation differed in the various animals. In general, however, following removal of the normally situated kidneys, there was an increase in blood flow through the explanted kidneys.[3] After a varying interval, the flows decreased somewhat to relatively stable levels between the pre- and immediately post-nephrectomy determinations. Definite enlargement of the explanted kidneys after removal of the opposite kidney was noted in four animals.

[3] Before the normally situated kidneys were removed, the blood flows through the explanted kidneys were estimated by assuming that one-half of the total urinary phenol red was excreted by each kidney. This assumption is not necessarily correct and, therefore, the blood flow determinations made prior to removal of the normally situated kidneys are not to be regarded as exact.

After a number of determinations of the blood flow in the explanted kidney were made in each dog, the renal artery was partially constricted. During the period before the onset of severe hypertension, the renal blood flows were essentially unchanged. The size and consistency of the explanted kidneys were not altered early in this period, but just before the onset of hypertension a decrease in size and firmness of the kidneys occurred in four of the animals. In one dog the renal blood flow was measured on the day before the blood pressure began to rise and was found to be markedly diminished. A similar reduction was noted in all the other animals shortly after the appearance of hypertension.

TABLE II

Summary of average results of phenol red and renal blood flow determinations made on all dogs during control, and early and late hypertensive periods

DOG NO.	CONTROL PERIOD						EARLY HYPERTENSION						SUCCEEDING PERIOD					
	Period of observation	Average arterial blood pressure	Renal blood flow		Phenol red excretion		Period of observation	Average B.P.	Renal blood flow		Phenol red excretion		Period of observation	Average B.P.	Renal blood flow		Phenol red excretion	
			No. of deter.	Average	15 min.	1 hour			No. of deter.	Average	15 min.	1 hour			No. of deter.	Average	15 min.	1 hour
	wks.	*mm. Hg*		*cc./ min.*	*per cent*	*per cent*	*wks.*	*mm. Hg*		*cc./ min.*	*per cent*	*per cent*	*wks.*	*mm. Hg*		*cc./ min.*	*per cent*	*per cent*
19	14	165/80	19	212	15.6	46.6	4	238/144	10	158	11.2	36.8	42	234/124	20	225	14.9	44.2
21	34	133/64	34	265	14.8	44.0	4	209/122	10	191	9.2	33.0	20	196/106	21	279	10.2	48.8
22*	13	142/69	25	281	13.1	41.5	4	257/141	6	200	12.5	39.6	2	267/161			0	10.0
23†	10	163/96	7	205	15.7	39.2	1	242/171	3	137	11.3	36.0	0					
35	9	167/77	12	252	18.6	51.3	3	235/137	11	191	5.7	35.3	6	219/132	13	233	15.9	48.3

The blood pressure recorded is the mean for the period. Phenol red excretion represents per cent of total amount injected.

* Died in uremia 6 weeks after clamping.

† Died in uremia 1 week after clamping.

In the dogs that survived, wide fluctuations in blood flow were noted for three to four weeks following the onset of hypertension (Figs. 1–3). The lower values were definitely below any of the control figures, but the higher ones were frequently within the normal range. Variations in size and consistency of the explanted kidneys were also noted during this period. Subsequently, an increase in the renal blood flow to the peroperative levels occurred. The frequent variations in size and consistency of the explanted kidneys, which were described above, also disappeared. In the two animals that died in uremia, there was a persistent reduction in renal blood flow. Table II shows the average results

in all of the dogs. Table III contains the figures for dye excretion, renal blood flow, extraction ratio and phenol red clearance in dog #35.

TABLE III

Summary of all results obtained on Dog #35 approximately 20 minutes after peak of dye excretion

DATE	B.P.†	URINE FLOW	APPEARANCE TIME OF PR IN URINE	PEAK OF EXCRETION OF PR AFTER INJEC.	PHENOL RED IN URINE	PHENOL RED CONCENTRATION**		EXTRACTION RATIO	PLASMA CLEARANCE	TOTAL RENAL BLOOD FLOW	TOTAL DYE EXCRETION		VOLUME OF PACKED RED CELLS
						Artery	Renal vein				15 min.	1 hour	
	mm. Hg	*cc./ min.*			*mg./ min.*	*mg./ cc.*	*mg./ cc.*	*per cent*	*cc./ min.*	*cc./ min.*	*per cent*	*per cent*	*cc. per cent*
2-13-39	158/83	1.0	2'15"	10'	2.19*	0.0402	0.0235	41	55*	224	19.1	53.1	41.5
2-28-39	165/82	0.5	2'10"	10'	2.20*	0.0384	0.0216	44	57*	228	17.8	52.2	42.5
3- 1-39	Left nephrectomy												
3- 3-39	162/77	0.7	2'50"	10'-15'	1.65	0.0332	0.0250	25	50	319	14.9	39.3	37.0
3-10-39	167/74	1.2	2'00"	10'	2.38	0.0419	0.0296	29	57	312	17.5	48.3	38.0
3-20-39	168/75	1.5	2'00"	10'	2.58	0.0385	0.0210	45	67	258	19.4	52.4	43.0
4-10-39	176/70	1.7	2'00"	10'	2.37	0.0360	0.0212	41	66	263	18.6	50.0	39.0
4-12-39	Right renal artery constricted												
4-14-39	188/93	1.3	2'30"	10'	2.48	0.0428	0.0268	37	58	295	18.7	51.5	40.0
4-21-39	261/145	1.0	8'10"	15'-20'	2.10	0.0406	0.0237	42	51	183	5.8	32.5	32.0
4-29-39	234/144	1.5	4'10"	10'	2.29	0.0447	0.0281	37	51	219	13.8	44.4	37.0
5- 8-39	204/116	1.0	22'00"	35'	2.18	0.0484	0.0248	49	45	153	0	29.6	40.0
5-17-39	245/156	1.3	6'00"	20'	2.70	0.0392	0.0209	47	69	245	8.9	48.0	40.0
5-24-39	196/130	0.5	24'00"	40'	1.81	0.0399	0.0273	32	45	212	0	26.5	33.0
5-31-39	215/124	1.5	2'00"	10'-15'	2.74	0.0470	0.0268	43	58	223	16.0	47.5	39.0
6-13-39	217/128	1.4	2'00"	10'	2.57	0.0441	0.0268	40	58	245	15.8	49.0	40.0

* Figures are for right kidney only (see footnotes on p. 210).

** Only the determinations recorded 16' to 23' after the peak of dye excretion have been included.

† All blood pressures given were taken during the experiments.

Effect of Pentobarbital on Blood Pressure and Renal Blood Flow

In order to determine to what extent the maintenance of normal renal blood flow is dependent upon the level of the arterial pressure in the chronically hypertensive dog, the blood pressure was reduced in three dogs by anaesthetizing them with pentobarbital, 30 mgm. per kgm. of body weight, being given intraperitoneally. The results, which are summarized in Table IV, were as follows:

Dog #19. In the prehypertensive period the average blood pressure was 165/80 and the average renal blood flow 212 cc. per min. The effect of pentobarbital was not tested during this time. In the period of chronic hypertension, the average renal blood flow was 225 cc. per min. Under

pentobarbital anaesthesia the blood pressure fell from 221/114 to 158/104 and the renal blood flow fell to 140 cc. per min.

Dog # 21. In the prehypertensive period the average renal blood flow was 265 cc. per min. Under pentobarbital anaesthesia the blood pressure fell from 142/65 to 114/47 and at the latter level of pressure the blood flow was 212 cc. per min. In the period of chronic hypertension the average blood flow was 279 cc. per min. Under pentobarbital anaesthesia the pressure fell from 220/120 to 188/96 and the blood flow fell to 173 cc. per min.

TABLE IV

Effect of pentobarbital on the blood pressure and renal blood flow

The control arterial pressure readings were made immediately before injection of pentobarbital, and those under anaesthesia during the renal flow determination. The renal blood flow figures are the mean of all the determinations made in the corresponding period.

DOG NO.	NORMAL				HYPERTENSION					P.P. ON RECOVERY
	Blood pressure (mm. Hg)		Renal blood flow (cc./min.)		Phenobarbital	Blood pressure (mm. Hg)		Renal blood flow (cc./min.)		
	Pre-anaesthesia	Anaesthesia	Pre-anaesthesia	Anaesthesia		Pre-anaesthesia	Anaesthesia	Pre-anaesthesia	Anaesthesia	
					mg./kg.					
21	142/65	114/47	265	212	30	220/120	188/96	279	173	272/170
35	180/90	131/72	252	216	30	238/137	190/112	233	185	268/176
					15	224/134	236/161	238	285	254/165
19	165/80		212		30	221/114	158/104	225	140	236/140

Dog # 35. In the prehypertensive period the average renal blood flow was 252 cc. per min. Under pentobarbital anaesthesia the blood pressure fell from 180/90 to 131/72 and at the latter level of pressure the blood flow was 216 cc. per min. In the period of chronic hypertension the average blood flow was 233 cc. per min. Under pentobarbital anaesthesia the blood pressure fell from 238/137 to 190/112 and the renal blood flow fell to 185 cc. per min.

In another experiment in this same dog during the period of chronic hypertension, only half of the previous dose of pentobarbital was given (15 mgm. per kgm., intraperitoneally), and the blood pressure, instead of falling, rose from 224/134 to 236/161. At the latter level of pressure the renal blood flow was 285 cc. per min.

These experiments indicate that when the blood pressure of the chronically hypertensive dog is reduced by pentobarbital anaesthesia, the renal blood flow falls considerably below the average normal level for the animal.

DISCUSSION

The foregoing experiments offer evidence which indicates that the Goldblatt type of chronic hypertension may not be associated with a permanent reduction in renal blood flow. During the early phase of the hypertension the renal blood flow was reduced, but after several weeks it returned to the control level. These observations do not conflict with those reported by Levy, Light and Blalock (3). The experiments of these authors were concerned chiefly with the period of the first three weeks after constricting the renal arteries. Although the renal blood flow was measured in two of their ten animals about two months after the original application of the clamps, they say that "when necessary the clamps were tightened in order to maintain the elevation in blood pressure." The time relation of the readjustment of the clamps to the blood flow determinations is not recorded. They also state that "in three animals in which the clamps were not adjusted between the second and third flows,. . . there was a slight increase in the renal blood flow and a slight decrease in the systemic blood pressure."

While the present study was being carried out, Corcoran and Page (8) reported that the clearance of phenol red was unimpaired in animals with experimental renal hypertension.

It is to be noted that in the calculations of renal blood flow in our experiments no account has been taken of the time required for the phenol red to pass from the blood stream to the bladder. Sheehan has assumed "that the dye content of the bladder represented, on the average, the dye extracted from the blood about six minutes earlier." Since this is only an approximation and may not be constant, it was believed that the validity of the calculations would suffer less if this correction were omitted. The calculated blood flows are therefore higher than they would have been had the lag been taken into account. Furthermore, no effort has been made to estimate how much of the dye excreted during the test periods had been stored in the renal intercellular spaces during the preceding high level periods. However, inasmuch as the observation

were made under similar experimental conditions, before and after the production of hypertension, the above mentioned factors should not affect the comparative value of the results.

SUMMARY

1. Arterial hypertension was induced in five dogs with single explanted kidneys by partial occlusion of the renal artery. Two dogs died in uremia 1 and 6 weeks, respectively, after application of the clamps. Three dogs survived and were killed 3, 7 and 11 months, respectively, after the clamps were applied.

2. Studies of the rate of urinary excretion of phenol red, and of the renal blood flow through the extraction of phenol red by the kidney, were made in these animals before and after the renal arteries were constricted.

3. Immediately before or coincident with the onset of hypertension, a reduction in renal blood flow and phenol red excretion occurred. After 3–4 weeks the renal blood flow returned to the control levels, but the hypertension persisted. In 4–7 weeks the phenol red excretion likewise returned to normal values.

4. These experiments indicate that chronic experimental hypertension of renal origin may persist after the renal blood flow has returned to normal.

5. Pentobarbital anaesthesia in these animals produced a fall in blood pressure and renal blood flow both before and after hypertension was induced.

PROTOCOLS

Dog # 19 Mongrel, female, 11–12 kg. Left kidney was explanted on November 10, 1937. Right nephrectomy was performed on January 10, 1938. Renal blood flow experiments were begun on March 29, 1938. Goldblatt clamp applied to left renal artery on July 6, 1938, was followed by only slight rise in blood pressure and no change in renal blood flow. Clamp was tightened on July 22, 1938, with moderate oliguria for 36 hours, and appearance of hypertension of plus 65 mm. Hg systolic and 55 mm. Hg diastolic. Renal blood flow values were reduced for three weeks. On August 12, 1938, blood flows returned to prehypertension levels, where they remained for the succeeding 10 months. Hypertension became less severe about September 20, 1938, but the blood pressure remained elevated at least 40 mm. Hg systolic and 30 mm. Hg diastolic above control base-line. The dog was killed on June 28, 1939. At autopsy the heart weighed 155 grams.

Kidney weight was 40 grams, 12 grams more than normal right kidney had weighed. The medulla was a little narrowed. Renal vein was normal. Artery was slightly thickened where the clamp had been applied. Only moderate constriction was present. Ureteral artery was twice normal size. One small artery entered kidney through capsule at lower pole.

Dog #21. Mongrel, female 12–13 kg. Left kidney was explanted, and renal vein isolated on January 4, 1938. Right nephrectomy was performed on February 4, 1938. Definite hypertrophy of left kidney followed this operation. Renal blood flow determinations were begun in March, 1938, and showed rather marked fluctuations. Left renal artery was constricted on December 9, 1938, and there followed a slight rise in blood pressure for 18 days. On December 28, 1938, there was a sudden increase in blood pressure of 85 mm. Hg systolic and 75 mm. Hg diastolic. Hemorrhages and localized arterial constriction were noted in one eye, retinal detachment in the other. Renal blood flow was reduced about 40 per cent but showed much variation from one experiment to another. Blood pressure likewise fluctuated from marked to moderate elevation. By January 20, 1939, renal blood flow was normal. Hypertension of plus 50 mm. Hg systolic and 30 mm. Hg diastolic persisted from this time on. Changes in the retinae disappeared except for persistent narrowing of the arteries in the eye which had had the detached retina. The dog was killed on June 28, 1939. Heart weight, 135 grams. Left kidney weighed 42 grams, 10 grams more than right kidney. Cortex was normal in thickness. Medulla was slightly narrowed. Renal vein was normal. Renal artery was slightly thinned where surrounded by clamp but there were no changes in intima. Ureteral artery was of normal size, with no collaterals through capsule.

Dog #22. German sheperd, female, 12.5 kg. Left kidney was explanted on January 14, 1938. Right nephrectomy was done on February 9, 1938, followed by hypertrophy of left kidney. Blood flow determinations were begun on May 9, 1938. Left renal artery was clamped on August 5, 1938. This was followed by the slow appearance of hypertension and steady reduction in renal blood flow. Severe hypertension of plus 100 mm. Hg systolic and 65 mm. Hg diastolic was present on September 16, 1938, when renal blood flow was 30 per cent reduced. Increasing elevation of blood non-protein nitrogen with clinical picture of "malignant phase" of hypertension was noted. Death with convulsions and non-protein nitrogen of 216 mg. per 100 cc. occurred on September 22, 1938. At autopsy the renal artery was narrowed within the clamp by thickening and sclerosis of arterial wall. No thrombosis was found and a small opening was still present through the artery. No collateral circulation was seen in the capsule or hilus. Renal vein was normal.

Dog #23. Mongrel terrier, female, 10 kg. Left kidney was explanted on January 7, 1938. Right nephrectomy was done January 31, 1938, followed by hypertrophy of left kidney. Renal blood flow studies were begun on March 15, 1938. Left renal artery was constricted on June 13, 1938, and hypertension of plus 70 mm. Hg systolic and 65 mm. Hg diastolic develop on the following day.

Renal blood flow was reduced 34 per cent. Sudden anuria June 16, 1938, with rapidly rising blood non-protein nitrogen. The dog died on June 18, 1938. At autopsy an occluding thrombus was found in renal artery beneath clamp. Renal vein was normal. No collateral vessels.

Dog #35. Mongrel hound, female, 12.5–13 kg. Left kidney was explanted on September 27, 1938, and found to be about two-thirds of expected size. Right kidney, of somewhat larger than normal size, was explanted on November 2, 1938. Renal blood flow studies were begun on February 6, 1938. Left kidney was removed March 1, 1938, and showed fatty atrophy of the upper pole. Some hypertrophy of right kidney followed. Right renal artery was clamped on April 12, 1939, with slowly increasing hypertension, which became severe (plus 75 mm. Hg systolic and 70 mm. Hg diastolic) on April 21, 1939. Renal blood flow, on April 14, was slightly reduced; on April 21, it was further reduced. Fluctuations in renal blood flow, blood pressure and size of explanted kidney persisted until May 24, 1939. Blood pressure then became stabilized at moderate elevation of plus 55 mm. Hg systolic and 50 mm. Hg diastolic. Renal blood flows were slightly but not significantly, reduced at this time. The dog was killed on August 22, 1939. Kidney weight was 39 gms. Renal artery was unchanged within clamp. Vein was normal. No collateral circulation was found. Kidney was normal in appearance on cut section.

The authors are indebted to Dr. Louis K. Alpert for assistance in coordinating the manuscript of this report with the others which follow in this series.

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THE ROLE OF ALPHA HEMOLYTIC STREPTOCOCCUS IN PNEUMONIA[1]

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There is no uniform opinion as to the possible role of the alpha hemolytic streptococcus in pulmonary infections. A few scattered reports of its presence in empyema fluid always express doubt as to its significance. One thesis published in Paris, by J. L. Calmela, "Role du Streptococcus Viridans dans les Pleuro-pneumopathies", appeared in 1928. In that paper casual bacteriological studies on a small group of cases varying from lung abscess and bronchiectasis to "pleuro-pneumonia" provide no evidence of this organism's etiological activity. During the influenza epidemic of the First World War, reports were published of bacteriological examination of cases of influenzal pneumonia, particularly at Camp Meade, Maryland, where this organism was a frequent finding in the sputum. In the literature of that time this organism was sometimes spoken of as the "Mather streptococcus", and it was found in cases which occurred around Chicago. The importance of this organism was obscured by the misconception that it might be the cause of epidemic influenza. After the World War bacteriologists studying respiratory disease came to regard streptococcus viridans in sputa as an unimportant mouth contaminant.

Experience with a fatal case at Fort George G. Meade and the discovery of several similar unpublished cases has caused me to reconsider this problem and to offer some new evidence in favor of a possible important pathogenic role of the streptococcus viridans in some cases of pneumonia.

CASE I

Three days before onset the patient competed in a boxing match of three rounds. As he was not in training, he was greatly fatigued by the exertion. Two days later, the day before admission to the hospital, he felt tired and stiff and generally

[1] Read before the Interurban Clinical Club, December 5, 1941.

[2] Lt. Col. Worth Daniels, M.C., supplied me with records of civilian cases used in this report.

weak. On admission, on May 19, he complained of weakness and numbness in the hands and back. The past history was essentially negative. He had had frequent colds, and about three years before he had an attack which he thought was similar to the present one, when his doctor said that he over-taxed his strength in too much baseball and track.

Physical examination: Temperature 99.4°F. Pulse 72. Respirations 20. The face was slightly flushed, the conjunctivae were congested, the tongue was coated and the nose and throat showed catarrhal inflammation. The heart and lungs were normal. The nervous system was normal, except that the patient seemed very listless and said he was so tired he could not move around and that his hands were numb. The urine was normal, except for a trace of albumin. The blood counts were normal, except for a leucocyte count of 15,000 and differential

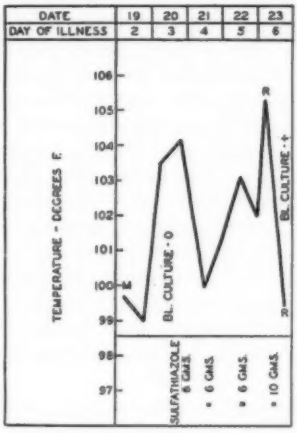

FIG. 1. Case I. May 1941. Fort George G. Meade

count as follows: juvenile neutrophils 4, stab forms 19, segmented neutrophils 63, lymphocytes 9, monocytes 2 per cent. The Wasserman was negative.

On the night of admission he had a shaking chill, and his temperature rose to 102°. Following this he started to cough and complained of pain in the chest. The following morning there were loud bronchial rales over the lower chest. Below the angle of the right scapula in the upper part of the right lower lobe the voice sounds were nasal and whispered voice sounds were increased. The sputum was gray, purulent and contained very little mucus.

A portable X-ray of the chest showed a mottled density, including linear shadows radiating from the right hilus and an exudative process occurring in the right cardiophrenic area indicative of atypical pneumonia. The remaining lung fields appeared essentially negative.

On May 20, 1941, sulfathiazole was given, 4 gm. in the initial dose and 1 gm. every four hours thereafter.

On the following day (May 21, 1941), the X-ray showed a slight increase in the changes at the right base. The sputum contained various organisms, prominent among them being alpha hemolytic streptococcus. In an Avery tube culture a pneumococcus, Type VI, was grown. Blood culture taken on May 20 was negative. On May 22, the diffuse bronchial rales were found increased but general weakness continued to be the patient's only important complaint. The spleen was palpable, as were glands in both axillae. The sputum consisted of a moderate amount of blood-streaked purulent material. Efforts to aid in evacuating the bronchi were without success. The white count was 8,300, of which 78 per cent were segmented neutrophils, 18 per cent lymphocytes and 4 per cent monocytes.

On May 23 cyanosis became a prominent feature, and the patient was placed in an oxygen tent. The physical signs in the chest were the same, except for the finding of many fine moist rales at the right base. The temperature rose to 105° rectal. In the tent he was much more comfortable, but the picture was one of anoxemia, due to bronchial obstruction with thick pus, which for some reason the patient felt too weak to expel. A roentgenogram of the chest showed no change. The white count was 8,750, with segmented neutrophils 80 per cent, eosinophils 2 per cent, lymphocytes 11 per cent and monocytes 7 per cent. The sulfathiazole blood level was 3.4 mgm. per 100 cc. Six grams of sodium sulfathiazole were given intravenously at 2 p.m. The condition remained unchanged. At 10 p.m. the temperature had dropped slightly to 103.6° rectally, but in other respects the condition was unchanged. He slept in short naps during the night. At 2 a.m. May 24, the temperature was 101.2°. At 5 a.m. the mucus in the throat increased and the difficulty with breathing was greater. He continued to take fluids well. At 7:45 a.m. he suddenly became noticeably more cyanotic and respirations ceased.

Post mortem examination made May 24, 1941, at 10 a.m., by 1st Lt. Theodore E. Woodward, M.C.:

External Examination: The body is that of a white young male, slender build, about 20 years old, weight about 135–140 pounds pounds and 5 feet 10 inches in length. Postural lividity is present. Rigor mortis has not become established. There is no evidence of any skin rash; however, there are some bluish colorations around the throat. The pupils are equal and symmetrical.

Abdomen: Upon incision there is a moderate amount of yellow fat. The muscles are well developed and there is very little free fluid. The liver extends 4 finger breadths below the costal margin, is deep purple in color; the spleen is definitely enlarged. The abdominal viscera otherwise appear normal.

Thorax: When the chest plate is removed and the mediastinum exposed, the lungs appear pink and inflated, and there is no evidence of fluid in either pleural cavity. The heart and lungs are in normal position. There are multiple thick and elastic pleural adhesions posteriorly in the right lower lobe. There are no adhesions on the left side. The pericardium is smooth and glistening and there is

the normal amount of amber colored serum. The heart is seared and punctured, and 5 cc. of ventricular blood drawn for culture.

Right Lung: On removing the lung the main bronchus is found to be filled with thick purulent mucus, closely resembling frank pus. The upper lobe of the right lung is air containing. Cross section reveals slight congestion in the upper lobe and purulent material can be expressed from the bronchioles. The right lower lobe is deep red in color, cuts with increased resistance and is the site of broncho-pneumonia. Purulent materials is expressed from all bronchioles in this lobe and also from the middle lobe.

Left Lung: Essentially air containing, the lung is normal in color. The main bronchus is found to be filled with purulent material. The cross section reveals a minimal amount of edema, but purulent material can be expressed from the small bronchi.

Heart: The muscles are of normal color and width, and there is no evidence of arterio-sclerosis in any of the coronary vessels. The right and left ventricle are of normal size and no abnormalities are noted in the right or left auricle. The semilunar valves are essentially normal. The muscles are of normal consistency, there is no evidence of infarct emboli or of pre-mortem clots. The valves are thin, elastic, normal in consistency and show no evidence of vegetation.

Anatomical Diagnoses: 1. Bronchitis, acute, purulent, diffuse; 2. Broncho-pneumonia, right lower and middle lobes. Post mortem cultures from heart's blood and bronchial exudate: In a direct examination of material from both sources, no bacteria or other organisms were seem.

Heart Blood: Cultures were made on blood agar plates and thioglycollate medium on May 24. On May 25, tiny alpha hemolytic colonies were present on the blood agar plates incubated either aerobically or in reduced oxygen (CO_2). By smear of the colonies gram positive cocci in pairs and chains were found. Isolated colonies were transferred to tube media. Thioglycollate media contained large numbers of streptococci in long and short chains. These were plated in blood agar, and in 24 and 48 hours alpha type hemolytic colonies with greenish zones were present. Gram's stain showed gram positive cocci in chains.

Study of these organisms in pure culture based upon the Blakes simplification of the Holman classification indicated *Streptococcus mitis:*

1. Alpha type hemolysis of deep colonies in blood agar prepared from pork infusion base with 0.8 per cent human blood.
2. Fermentation of salicin and lactose.
3. No fermentation of mannite or inulin.
4. Organisms were not bile soluble and did not show capsular swelling in any of the XXXII types of pneumococcus antisera.

Exudate from bronchus: This material was inoculated in blood agar plates and thioglycollate medium. The blood agar plates remained sterile for 10 days. Gram positive cocci in pairs and chains were isolated from thioglycollate medium after 24 hours incubation and after plating and re-isolation were found to be

Streptococcus mitis by the same criteria as used in identifying the organisms from the heart blood.

No other bacteria were found from either source. (Capt. Roger D. Reid, S.C.).

Microscopic report on the tissues, by Colonel J. E. Ash, M.C., Curator of the Army Medical Museum:

Lungs: Three sections show a fairly characteristic picture throughout. The medium sized and smaller bronchi and some of the bronchioles are filled and distended with purulent exudate. The pseudo-stratified columnar epithelium of the bronchial tree shows partial ulceration and its desquamated products can be seen in the lumens, mixed with the purulent exudate. The bronchial walls and the interstitial tissue immediately about them for some distance are densely infiltrated by lymphocytes, mononuclear leucocytes and plasma cells, contrasting with the purulent exudate in the bronchial lumens. Relatively small numbers of polymorphonuclear leucocytes are seen peribronchially. The mononuclear infiltration extends from these peribronchial areas. Some of the alveolar lumens contain blood mononuclear cells and desquamated alveolar lining cells. Edema fluid and heart-failure cells are present in some alveoli, but there is no fibrin.

Comment: The lesion in the lung conforms very well to the picture of interstitial pneumonia, described particularly in influenza.

Our interest was aroused by finding no organism other than streptococcus viridans in the heart's blood and bronchial secretion at post mortem. Shortly after studying this case, I learned of a similar case that had been carefully observed by Dr. Worth Daniels in Washington in 1938.

CASE II

A 46-year old business executive was first seen on December 28, 1937. He had felt unusually fatigued for about two days and gradually developed a respiratory infection, consisting of a typical head cold and sore throat. On December 28 he had slight fever and chills. At this time the pulse was 100 and markedly irregular, due to premature contractions. The blood pressure was 170/100. Gallop rhythm could be heard at the apex of the heart. Aside from coryza and mild injection of the pharynx there were no abnormal findings in the respiratory tract. There was no cough. There were no basal rales nor was there liver enlargement. The following day the patient's temperature had risen to 102°. He complained of headache, and a slight, mild, productive cough developed, but there were no abnormal lung findings. On this day the leucocyte count was 6,600 and there were 70 per cent polymorphonuclear neutrophils. The next day there was no change, but when seen on December 31 the patient complained of an increase in cough and it was obvious that his condition was not as good as at previous occasions. The rate of respiration had increased and there was moderate dullness

and suppression of breath sounds over the right lower axilla. The temperature was 102°. The patient was admitted on the third day of his illness to The Emergency Hospital, Washington, D. C., where a radiographic film of the chest was reported as follows: "Examination of the chest shows a fairly large area of consolidation near the right hilum in the middle third of the right lung. The appearance is that of an inflammatory process most probably in the right middle lobe." At this time there was a paroxysmal cough productive of considerable amounts of purulent sputum containing blood. Typing failed to reveal any of the types of pneumococcus for which antiserum is available. Culture of the sputum yielded streptococcus viridans. On that evening moderate cyanosis of the nail beds developed

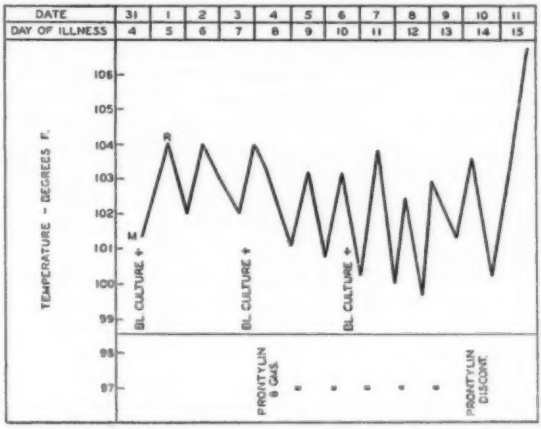

FIG. 2. Case II. Dec. 1937—Jan. 1938. Emergency Hospital, Washington, D. C.

and dullness with suppression of breath sounds and a few rales was noted over the right lower lobe.

During the first three days in the hospital he seemed in good condition. When the blood culture taken December 31, on the fourth day of his illness, was reported on January 3 to contain streptococcus viridans treatment with prontylin, 90 grains daily, was begun. Cyanosis became more marked and on January 4 the patient was placed in an oxygen tent. As the illness progressed, cough became more paroxysmal and productive of large quantities of muco-purulent and often blood tinged sputum. Gradually patchy signs of solidification developed over the entire right chest and a roentgenogram of the chest on January 3 was reported as follows: "Portable examination of the chest shows the inflammatory process in the right lung to be a little more extensive than at the last examination. The process now apparently involves the three lobes."

The second and third blood cultures, on January 3 and 6, yielded "a Gram-positive coccus growing in long chains. It is not hemolytic and the colonies are green on blood agar. The organism shows no swelling on typing with pneumococcus sera I, II, III, V, VII, VIII, and XIV. Inoculation in mice does not kill the animals and in peritoneal smears there are numerous pus cells and macrophages, containing typical streptococci. Diagnosis: Streptococcus viridans."

During this period the patient was chilly at intervals and occasionally had a shaking chill. The paroxysms of coughing became severe and in these episodes the patient would lose his breath and develop an almost black cyanosis. At intervals he would awaken from sleep sometimes gasping for breath, coughing, but unable to bring up any sputum. At this time restlessness would be marked, his expression would become anxious, delirium was striking and he would beat frantically at the sides of the oxygen tent. On these occasions cyanosis would be extreme. Often by the use of an aspirator some material could be aspirated from the pharynx with some relief. These episodes became more frequent and more marked, and persistent dark cyanosis was present. Between the suffocating attacks there was stuporousness alternating with extreme restlessness and delirium. On January 9 slight jaundice of the sclerae was noted and the urine contained bile. The prontylin was continued from January 3 through January 9 in dosage of 90 grains daily and was given with an equal amount of sodium bicarbonate. On January 7 the CO_2 combining power was 63 per cent and the non-protein nitrogen 35 mgm. per cent. Prontylin was discontinued because there had been no evidence of improvement during its administration. Gradually the patient became worse and died on January 11, the sixteenth day of the illness.

TABLE I

Blood Counts—Case II

DATE	R.B.C.	HB.	W.B.C.	POLYMORPH. NEUTROPHILS	LYMPHOCYTES	MONOCYTES
		gm.		*per cent*	*per cent*	*per cent*
12/31/37			11,800	77	18	5
1/ 1/38			11,100	69	20	11
1/ 2/38			11,600	72	21	7
1/ 3/38			9,300	87	11	2
1/ 4/38	4.38	14	10,400	84	14	2
1/ 5/38			10,800	78	20	2
1/ 6/38						
1/ 7/38			14,600	70	4	
1/ 8/38			15,400	74	8	
1/ 9/38						
1/10/38	3.63	11	17,800	75	5	1

Autopsy (*Dr. C. G. Aronstein*). Body is that of a white male in the latter half

of the 5th decade of life, well developed and nourished. Hair is black, with slight graying, especially at the sides. Pupils equal and moderately dilated. Sclerae show icterus and a few petechial hemorrhages in the conjunctiva of the lower lids. Lips and nail beds cyanosed. Abdomen is not distended. Subcutaneous fat is well preserved and about 2–2.5 cm. thick.

Heart: Enlarged and very firm. Culture taken from the right ventricle. On opening the heart, no dilation is evident. The valves are smooth and normal throughout. Coronaries and aorta show atheromatosis. Myocardium is light pink in color, resembling fresh salmon color.

Lungs: There is no free fluid in either half of the chest cavity. No adhesions are encountered. On removal the posterior half of the upper lobe, the posterior three-fourths of the middle lobe and practically the entire lower lobe on the right side are found consolidated. The left lung shows complete consolidation of the lower lobe. On section of the consolidated lung tissue it seems to be deeply congested, edematous and of a different consistency from that of pneumococcal pneumonia. There is no resemblance to either red or gray hepatization. The cut surface is irregularly lobulated and resembles dark red velvet, instead of the relatively smooth and dry cut surface of ordinary pneumonia. In addition thick creamy yellow and white pus exudes from the cut bronchioles throughout. At the lower margin of the right lower lobe there is a very hard area about 4 cm. square, which resembles an infarct. The bronchi and their primary radicles show extensive inflammatory reaction with congestion and edema of the mucosa and much thick yellow pus. Examination of the pulmonary arteries shows atheroma of both. In addition there is a large organized and slightly adherent thrombus in the right artery, which has plugged two large primary divisions by bending on itself in the shape of a "U." Another smaller thrombus, also organized, is found in a branch proceeding to the upper lobe. Between the consolidated and normal tissue of the upper right lobe a line of nodules is palpable in the lung tissue and on section of one of these it is found to be very pale, pinkish, yellow and edematous. It resembles attempted organization. These nodules are 1–1.5 cm. in diameter. One has a congested central portion.

Liver: Normal in size and, on section, diffusely mottled with yellow. Gall bladder and ducts negative.

Spleen: Enlarged and somewhat soft. On section the cut surface bulges. The pulp is congested and mushy.

Kidneys: Normal in size, congested. Stellate veins of surface prominent. Fetal lobulations retained. Cut surface shows cortex of average depth. Yellow streaking of cortex is the only abnormality.

Adrenals and Pancreas: Congested.

G. I. Tract: Stomach is distended with gas. Remainder of tract is negative.

Bladder and Prostate: Negative.

Histologic Findings (R. D. Lillie, Senior Surgeon, National Institute of Health).

Adrenal: Shows few small foci of interstitial lymphocyte infiltration in cortex and medulla in both of two blocks.

A small thrombus is composed centrally of red corpuscles, peripherally of quite densely matted fibrin. May be an embolus.

Pancreas: There is one focus of moderately dense interlobular lymphocyte infiltration. Parenchyma and islets are normal but partially autolyzed.

Lung: First section shows quite marked irregular alveolar exudation, variable in character; in some places hemorrhagic or serosanguineous in character, or composed of serum, red corpuscles and monocytes with fewer lymphocytes and plasma cells and phagocytic macrophages. There are a few alveoli with serosanguino-purulent exudate. There is patchy perivenous and interstitial lymphocyte infiltration of moderate density. Pleura shows moderate anthracosis and moderate irregular, early, dense, lymphocyte infiltration. Second lobe shows patchy consolidation, exudate is composed of red cells, fibrin and lymphocytes and there are some fusiform fibroblasts. In other parts the exudate is predominantly monocytic with some lymphocytes, red corpuscles and a little fibrin or serum mixed in. Such areas show moderate interstitial and perivenous lymphocyte infiltration and some anthracosis. A third section shows extensive hemorrhage in the alveoli with some necrosis of septa and hemolysis of the exudate. There are a few patches of purulent exudate possibly in atria. There are a few alveoli showing fibrino-hemorrhagic exudate in which there are a few fusiform fibroblasts. Fourth section shows hemorrhagic exudate in alveoli with some areas of septal necrosis and hemolysis. Fifth section: There is patchy alveolar exudation, in places hemorrhagic or serosanguinous with few patches of dense purulent exudate. Sixth and seventh sections show patchy consolidation in which there is purulent bronchial exudate, much dense fibrin in alveoli, some of which contains red corpuscles, and much organization of this fibrin by proliferating fibroblasts and some lymphocytes, accompanied by interstitial lymphocyte and plasma cell infiltration. There are also areas in which alveoli are filled with proliferating fibroblasts without any included fibrin.

Heart: Sections show no significant lesions.

A large artery is negative.

Kidney: Shows few foci of perivenous lymphocyte infiltration in the cortex. There is slight autolysis of tubules.

Liver: Shows capillary congestion and moderate periportal lymphocyte infiltration. No other significant lesions.

Spleen: The follicles are small and inactive. The pulp is congested and shows quite marked irregular infiltration by lymphocytes, large lymphoid cells and plasma cells.

Comment: This is a subacute, monocytic and organizing and partly interstitial bronchopneumonia, accompanied by subacute splenitis with some areas of acute hemorrhagic pneumonia or possibly pulmonary infarction. There is some general resemblance to the pneumonias of psittacosis, Q fever and possibly other virus pneumonias. I would not care to express any definite opinion as to the etiology of this pneumonia without data as to duration of disease at the time of death of the patient. Organization of alveolar exudate, while not the usual thing in ordinary bronchopneumonia, is not particularly unusual. The characteristic of

the Q fever pneumonia is that this organization appears quite early in the course of the disease, perhaps as early as five or six days from onset.

This case was thought to be one of broncho-pneumonia of unknown etiology complicated by secondary infection with streptococcus viridans. This opinion was given further support by the fact that one of the nurses who had cared for this patient was taken ill two days after his death with atypical broncho-pneumonia, which lasted about three weeks. Her history is summarized below.

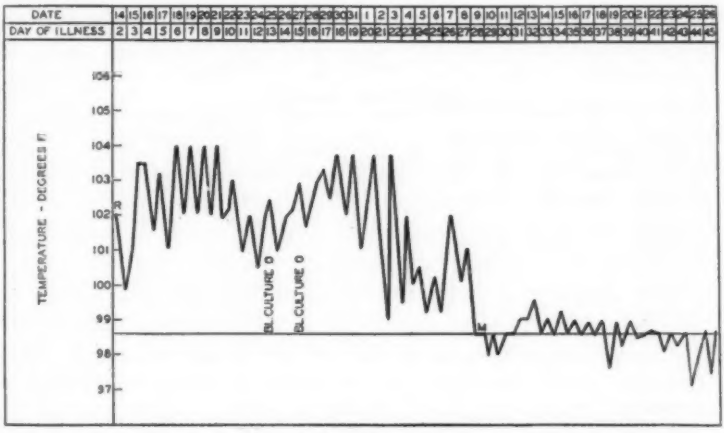

FIG. 3. Case III. Jan. 1938—Feb. 1938. Emergency Hospital, Washington, D. C.

CASE III

On January 12, 1938, the day after the death of the second patient we are reporting, his nurse felt tired and stayed at home, sleeping most of the day. In the afternoon of the next day she felt chilly and weak and her temperature was found to be 101.8°. She took aspirin at bed time, slept well, but experienced several sweats during the night and was bothered by a cough. On the morning of January 14 she developed a slight occipital headache and the fever continued. She was admitted to the hospital. Physical examination revealed a temperature of 102.2°, pulse 112, respiration 22, blood pressure 108/68, and white blood count 6,700. The urine was normal. There was a frequent loose cough. The conjunctivae were injected. The lungs were clear. A specimen of sputum on Jan 16 showed no pneumococci and only a few streptococci of the viridans type. In the sputum on Jan. 20 the predominating organism was streptococcus viridans.

Blood Cultures on Jan. 25 and 27 were sterile. A portable X-ray on Jan. 15 showed "a fairly extensive area of broncho-pneumonia on the left side between the 2nd, 3rd and 4th ribs anteriorly. The right lung appears clear. There is no evidence of pleural effusion."

The patient complained of severe pain in the left lower chest posteriorly on Jan. 16. The cough became more frequent and on Jan. 17 it was productive of yellow muco-purulent material, which was described as quite foamy. On the 18th the sputum was blood streaked and thick and very large in amount. On Jan. 20 the patient was delirious. The thick, stringy sputum contained no pneumococci and the predominant organism was streptococcus viridans. Two days later the white blood count had risen to 11,500 and her condition was critical. The next day cyanosis was present and she was placed in an oxygen tent with apparent

TABLE II

Blood Counts—Case III

DATE	R.B.C.	HB.	W.B.C.	PMN	LYMPHS.	MONOS.
		gm.		*per cent*	*per cent*	*per cent*
1/15/38	3.86	11.5	6,700	70	27	3
1/17/38			6,800	67	30	3
1/19/38	4.70	14.5				
1/20/38			10,400	79	16	5
1/22/38			14,500	85	12	3
1/24/38			16,000	88	10	2
1/26/38			17,400	87	11	2
1/27/38	3.89	11.5				
1/28/38		13.5				
1/29/38			7,700	74	24	2
1/30/38			9,400	79	17	4
2/ 1/38	4.80	13.5	15,000	86	10	4
2/ 9/38			6,100	73	23	3

benefit. For the next eight days she was delirious, irrational, cyanotic when out of the tent, unable to void, and coughing up huge amounts of greenish yellow, occasionally blood streaked, mucoid sputum. Blood cultures on Jan. 25 and 27 were negative. The leucocyte count increased to 17,400 on Jan. 26. Gradually she improved and by February 1 was definitely better. During the next week the temperature became spiking and gradually lower. Exhaustion and mental depression were extreme, and the abundant sputum became foamy, although still occasionally blood-streaked. Portable X-rays showed spread of the process to the left lower lobe and also coalescing broncho-pneumonia of the right lower lobe. On January 27 the picture was essentially unchanged. On February 2 the right lung was clearing, but the left seemed more involved. On February 24 there was still slight infiltration in the lower right lobe and at the left border of the heart.

After a long convalescence she was discharged well on February 26. At no time during her illness was specific medication resorted to.

DISCUSSION

We have then, a case (Case II) pathologically characteristic of so-called primary atypical broncho-pneumonia and closely resembling influenza pneumonia, in which the streptococcus viridans entered the picture early enough to be found not only in the sputa, but also in the blood stream on the fourth day of illness, and another more fulminating case (Case I) in which death occurred on the sixth day of illness. In this case the streptococcus viridans was found in the sputum during life, and in the lung and heart's blood at autopsy two hours and a quarter after death.

One is led to wonder as to the role played in these cases by the omnipresent, alpha hemolytic streptococcus (viridans). Kneeland and Smetana (1), in their description of cases of atypical pneumonia which occurred at the Presbyterian Hospital in New York, reported that the streptococcus viridans was the predominant organism in the sputa of most of their cases. They say, however, that this was probably without significance, since in their laboratory over a period of years it was the usual finding in sputum from a great many normal persons. The one patient reported in their group who died, at autopsy showed bronchioles filled with pus from which pneumococcus type X was grown. Kneeland and Smetana concluded that, whereas this organism hardly could have played a part in the pneumonia, it undoubtedly was important as a factor producing death.

The impressions I gained in watching our patient (Case I) were, first, that weakness was unusually marked and, second, that he more or less suffocated from occlusion of the bronchi and bronchioles. The same may be said of Case II, and the pathological picture in both cases also suggests this. It seems probable that the streptococcus viridans may have played a role similar to that played by the pneumococcus type X mentioned by Kneeland and Smetana in the production of suffocating purulent bronchitis. The same might be said concerning one of the two fatal cases of (primary) atypical broncho-pneumonia reported by Longcope from the Johns Hopkins Hospital (2). From the other fatal case all post mortem cultures were sterile and ferret and mouse inoculations revealed no evidence of virus infection. In this case "the bronchi

everywhere were filled with a very thick exudate consisting of about half polymorphs and half round cells".

The pathological lesion of influenza consists primarily of an intense necrotizing inflammation of the trachea, bronchi, and, especially, the bronchioles. Cases of influenza in the 1918 epidemic (3), in which death occurred early in the disease, that is, in a few days, showed this type of lesion, which was accompanied by filling of the lungs with serosanguinous exudate and by extreme congestion of the capillaries. Cases terminating fatally a few days later showed secondary infection with organisms which were opportunist pathogens present in the mouth. These secondary invaders varied in different localities. The influenza bacillus was widely encountered. In Illinois a virulent type of pneumococcus was reported, in Mississippi a staphylococcus aureus and elsewhere the beta hemolytic streptococcus prevailed. At Camp Meade, Maryland, Captain George Mathers died of influenza pneumonia before he was able to report his bacteriological studies. These were alluded to by Dr. Ruth Tunnicliff (4), Contract Surgeon, U.S.A., in the Journal of the American Medical Association, November, 1918. From 110 cases of influenza and pneumonia, Captain Mathers isolated a green-producing streptococcus from the sputa in 87 per cent on the first and second day of disease. The influenza bacillus was also isolated from 58 per cent of the sputum cultures. Jordan (5) found a similar green streptococcus in the majority of his cases in Chicago.[3]

SUMMARY

1. Two fatal cases of primary atypical broncho-pneumonia are reported. In one case streptococcus viridans was recovered from the sputum and from the blood stream during life. In the other case the

[3] Members of the Army Influenza and Pneumonia Commissions (6) studying primary atypical pneumonia at an Army Post early in 1942 isolated the alpha streptococcus in a very high percentage of cases from patients with atypical pneumonia, from patients with other diseases, and from normal controls. The incidence of the alpha streptococcus in the sputum and throat in the three groups was approximately the same. Cultures taken at bronchoscopy in cases of atypical pneumonia failed to reveal evidence that the alpha streptococcus played an important role in the pathogenesis of the disease. These studies are clear-cut but they do not rule out the possibility that in other environs and conditions strains of alpha streptococcus may be important pathogens in pulmonary disease.

organism was recovered from the sputum during life, and from the heart's blood and bronchial exudate at autopsy shortly after death.

2. The presence of streptococcus viridans in cases of influenza pneumonia and primary, atypical broncho-pneumonia has been noted previously, but its importance has been discounted. The observations in cases reported here suggest that this organism is capable of playing a pathogenic role as a secondary invader. In view of its well recognized pathogenic activity in the production of endocarditis, it may be that its presence in the bronchi in association with purulent inflammation is of more significance than present opinion recognizes. The cases presented here are reported with the purpose of directing attention to this possibility.

3. Intense, purulent bronchiolitis, by causing obstruction of the air passages, is an added factor in the symptomatology and outcome of atypical broncho-pneumonia, and the streptococcus viridans appears to be one of a variety of organisms which may produce this complication.

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RENAL OSTEOMALACIA AND OSTEITIS FIBROSA IN ADULTS

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That there is a close relationship between renal disease, osseous changes and parathyroid hyperfunction seems fairly well established both from experiments in animals (1) and from clinical and anatomical studies in humans (2, 3, 4, 5). Although the exact mechanism for such a relationship has not been fully elucidated, the rather rare cases of "renal rickets" or "renal osteitis fibrosa" make it clear that bone lesions of varying types may develop in the course of prolonged renal insufficiency. Whether such changes are due to secondary hyperparathyroidism, acidosis, increased alimentary phosphate excretion or other unknown factors are controversial points.

A few reports (4, 6, 7) would seem to indicate that one can recognize histological alterations in the skeletal system in cases of renal insufficiency in adults before they manifest themselves clinically or by x-ray examination. The present study was undertaken to determine the nature and the extent of such lesions in a series of routine autopsies on patients dying of chronic nephritis and to correlate, if possible, the pathological and clinical pictures.

MATERIAL AND METHODS

Sections of the vertebrae were studied in 39 adults dying of renal insufficiency. In addition the bones of 14 individuals dying of some acute surgical emergency (e.g., fractured skull) were examined as controls. We have also had an opportunity to examine 3 cases of "renal rickets" reported from this Hospital and one other unreported case.

The histological method used was to decalcify partially in nitric acid, imbed in celloidin and stain with hematoxylin and eosin. It should be pointed out that we have compared this method with that in which no decalcification is carried out, as recommended by McLean and Bloom (8) and have found the two to agree.

OBSERVATIONS

In Table I are found the results of our observations on 39 individuals dying of renal insufficiency. They have been divided into 3 groups

TABLE I

Summary of observations in 39 cases of renal insufficiency

AUTOPSY NUMBER	AGE, SEX, COLOR	DURATION OF SYMPTOMS OR SIGNS	BLOOD DETERMINATIONS						ANATOMICAL FINDINGS	DEGREE OF OSTEOID	DEGREE OF OSTEITIS FIBROSA
			Time before death	NPN	Serum protein	Serum calcium	Serum phosphorus	CO_2 comb. power			
				mgm. per cent							
16067	22, M W	4 yrs., oedema	4 yrs.	*	†			‡	Chronic glomerulonephritis, cardiac hypertrophy, rupture of aorta	3+	3+
16354	38, F C	3 yrs., high B.P.; 4 mo., P.S.P. 0	3 mos.	100	5.6	6.0	7.3	43.8	Chronic glomerulonephritis	3+	3+
			6 days	192	5.9	6.2	8.5	17.4			
16670	37, M W	2 yrs., high B.P.	7 mos.	76	6.1	8.8	7.3		Chronic glomerulonephritis, cardiac hypertrophy, gen. arteriolosclerosis	3+	1+
			6 mos.	100	5.2	8.1	8.9	36			
			5 days	160	5.2	9.2	11.4				
16768	28, F C	10 yrs., prog. renal failure	4 mos.	80		8.3	7.1	34.3	Chronic glomerulonephritis, sickle cell anemia, cardiac hypertrophy	2+	3+
15361	44, F C	3 yrs., dyspnea	3 yrs.	44	5.0	7.2	6.4	52.2	Chronic glomerulonephritis, cardiac hypertrophy	2+	2+
			4 mos.	82	7.4	9.4	6.0				
16040	29, M W	16 mos., headache; 6 mos., nycturia; 2 wks., oedema	4 mos.	160	5.5				Chronic glomerulonephritis, cardiac hypertrophy	2+	2+
15646	29, F C	18 mos., oedema	3 mos.	95	6.3	6.8	5.8		Chronic glomerulonephritis, cardiac hypertrophy	2+	1+
			1 mo.	160	6.0	6.9	5.8				
16777	16, M W	2½ yrs., prog. renal failure	10 mos.	76	6.3	10.7	7.6		Chronic glomerulonephritis, cardiac hypertrophy	2+	0
			5 mos.	139		6.8	8.9	40.9			
			1 mo.	200		7.3	14.0				
16504	21, M W	2 yrs., oedema	9 mos.	67	4.8	8.0	8.0	39.0	Chronic glomerulonephritis, cardiac hypertrophy	1+	0
			7 mos.	84	4.8	7.5	9.4	51.3			
			1 day	112	6.4	9.2	12.1	28.7			
16370	26, F W	2 yrs., prog. renal failure	3 mos.	50	5.9	8.3	5.7	43.8	Chronic glomerulonephritis, cardiac hypertrophy	0	0
			2 mos.	60	5.5	9.0	6.6	39.0			
			1 day	138	4.6	6.5	16.0	24.9			
16114	31, M W	5 yrs., albuminuria; 4 mos., oedema	1 day	248					Chronic glomerulonephritis, cardiac hypertrophy	0	0
15035	26, M W	2 yrs., prog. renal failure	1 mo.	104	4.0	8.0	10.8	33.8	Chronic glomerulonephritis, cardiac hypertrophy	0	0

* Steadily rising.
† Usually low.
‡ Always low.

TABLE I—*Continued*

AUTOPSY NUMBER	AGE, SEX, COLOR	DURATION OF SYMPTOMS OR SIGNS	BLOOD DETERMINATIONS						ANATOMICAL FINDINGS	DEGREE OF OSTEOID	DEGREE OF OSTEITIS FIBROSA
			Time before death	NPN	Serum protein	Serum calcium	Serum phosphorus	CO_2 comb. power			
				mgm. per cent							
16668	25, M C	3 mos., dim. vision and vomiting	2 days	335	4.7			10.0	Obstruction urethra, chronic pyelonephritis, cardiac hypertrophy	3+	3+
16906	22, M W	8 mos., prog. renal failure	6 mos. 1 day	160 232	5.7	9.6 6.3	5.3 12.5	48.5	Chronic pyelonephritis, arteriolosclerosis, cardiac hypertrophy	2+	1+
16865	46, F W	Cystitis, 5 yrs.							Carcinoma cervix, chronic cystitis, chronic pyelonephritis	2+	1+
17264	54, F C	9 mos., dyspnea	6 mos.	60				47.0	Chronic arteriolosclerotic nephritis, rt., tuberculous lt. kidney with occlusion of ureter	3+	3+
16981	58, M W	11 mos., high B.P.	6 mos. 5 mos. 2 wks.	100 62 128	6.3 7.2	8.4 9.5	4.4 4.7		Chronic arteriolosclerotic nephritis, cardiac hypertrophy	3+	1+
15790	31, F C	1½ yrs., high B.P.	9 days	152				52.2	Arteriolosclerotic nephritis, cardiac hypertrophy	2+	1+
16834	44, M C	2 yrs., high B.P.	3 days	216	7.4	6.6	11.3	33.4	Operative absence of left kidney, arteriolosclerotic nephritis of rt., cardiac hypertrophy	2+	0
16812	37, F C	18 mos., oedema and vomiting	8 days	136	6.6	8.8	14.5	68.3	Arteriolosclerotic nephritis, cardiac hypertrophy	2+	0
16688	56, M W	2 mos., high B.P.	4 days	215	6.0	5.5	10.0	28.7	Arteriolosclerotic nephritis, cardiac hypertrophy	2+	0
16715	53, M W	1 yr., high B.P.	4 days	144		9.0	10.8	40.0	Arterio- and arteriolosclerotic nephritis, cardiac hypertrophy	1+	0
16028	47, F W	2 yrs., high B.P.	2 days	100	7.4	10.5	6.1	42.1	Arteriolosclerotic nephritis, cardiac hypertrophy	0	0
16956	31, M C	8 yrs., high B.P.	3 days	192				39.0	Arteriolosclerotic nephritis	0	0

TABLE I—*Concluded*

AUTOPSY NUMBER	AGE, SEX, COLOR	DURATION OF SYMPTOMS OR SIGNS	BLOOD DETERMINATIONS						ANATOMICAL FINDINGS	DEGREE OF OSTEOID	DEGREE OF OSTEITIS FIBROSA
			Time before death	NPN	Serum protein	Serum calcium	Serum phosphorus	CO_2 comb. power			
				mgm. per cent							
15691	41, F C	3 yrs., high B.P.	1 day	248	6.1	9.6	18.8	35.3	Arteriolosclerotic nephritis, cardiac hypertrophy	0	0
15823	33, M W	13 yrs., oedema and albuminuria	16 days	150	6.4	8.2	10.5	35.5	Arteriolosclerotic nephritis, cardiac hypertrophy	0	0
15902	38, F C	6 wks., dyspnea	14 days	112	6.0				Arteriolosclerotic nephritis, cardiac hypertrophy	0	0
16827	36, F C	8 yrs., high B.P.	3 days	132	6.3	8.6	10.0	55.1	Arteriolosclerotic nephritis, cardiac hypertrophy	0	0
16843	38, M C	7 yrs., high B.P.	13 days	116	5.8	8.6	7.0	46.6	Arteriolosclerotic nephritis, cardiac hypertrophy	0	0
16097	34, M W	1 mo., poor vision	6 days	104	6.6	9.2	9.0	55.1	Arteriolosclerotic nephritis, cardiac hypertrophy	0	0
16207	32, F C	10 yr., high B.P.	14 days 4 days	106 220	6.9 6.7	9.0 8.5	7.5 18.0	54.1 42.8	Arteriolosclerotic nephritis, cardiac hypertrophy	0	0
16245	55, M C	4 yr., high B.P.	4 mos.	74	6.8			44.0	Arteriolosclerotic nephritis, cardiac hypertrophy	0	0
16257	36, F W	1 mo., dim. vision	26 days 2 days	80 150	7.1 6.9	9.7 9.1	7.3 11.6	74.0 40.0	Arteriolosclerotic nephritis, cardiac hypertrophy	0	0
16606	24, M C	1 yr., high B.P.	5 days	132	7.1			40.0	Arteriolosclerotic nephritis	0	0
16850	27, F C	2 mos., dim. vision	8 days 2 days	64 280	6.9 6.1	10.4 8.7	5.7 9.3		Arteriolosclerotic nephritis, cardiac hypertrophy	0	0
15689	37, M C	2 mos., dim. vision	1 mo. 1 day	60 270	6.9			21.1	Arteriolosclerotic nephritis, cardiac hypertrophy	0	0
16814	15, F C	1 mo., oedema	5 days	132	5.4	9.5	7.3	42.8	Arteriolosclerotic nephritis, cardiac hypertrophy	0	0
16751	37, M W	10 mos., high B.P.	9 days	112	5.8			48.5	Arteriolosclerotic nephritis, cardiac hypertrophy	0	0
15052	41, M W	2 yrs., high B.P.	20 days	114	5.5			49.8	Arteriolosclerotic nephritis, cardiac hypertrophy	0	0

on the basis of the kidney lesions; *i.e.*, chronic glomerulonephritis, chronic pyelonephritis and chronic vascular nephritis. The approxi-

mate duration of the disease as ascertained by the symptoms and signs presented by the patient and the serum non-protein nitrogen, protein, calcium, phosphorus and CO_2 combining power at various times before death are also summarized.

Two changes in the skeletal system have been tabulated: the amount of osteoid tissue and the extent, if any, of osteitis fibrosa. When present, osteoid tissue appears as a pink border or band along the traveculae, the ossified portions of which stain more deeply because of their lime salt content. Osteoid in the normal adult individual is usually absent or very scanty and its presence in any quantity indicates that lime salts are not being deposited in normal fashion. We have graded the amounts present as 1, 2 or 3 plus. The changes of osteitis fibrosa, which were slight when compared to those that are encountered in primary hyperparathyroidism, consisted of areas along and within the traveculae where increased bone destruction was taking place. Such foci are erosions of the bone; in such a space there are osteoblasts, osteoclasts and connective tissue cells. In the larger ones blood vessels are also present. In none of the cases was the change severe enough to show any replacement of the marrow spaces by connective tissue such as is seen in the bones in extensive von Recklinghausen's disease.

It will be noted that excessive osteoid was present in 9 of the 12 cases of glomerulonephritis while the changes of osteitis fibrosa were present in 7. No correlation could be found between the degree of bone change and either the clinical duration of disease or the levels of the serum chemical constituents.

In the 3 cases of pyelonephritis, osteoid in excess was found in all; the lesions of osteitis fibrosa were seen in each also.

In 24 cases of chronic vascular nephritis excessive osteoid was encountered in 7. Changes characteristic of osteitis fibrosa were seen in 3 of these. Again, both in this group and in the preceding one, the information regarding the duration of the disease and chemical changes in the blood was of no value in determining whether skeletal changes would or would not be found.

In the 14 control cases excessive osteoid was found in only 1 instance; in this individual, living 3 days after a fractured skull, there was enough to be graded as 2+. The explanation for its presence in this case is not clear since the body was well nourished at autopsy.

DISCUSSION

The above observations would seem to indicate that in a group of adults dying of chronic renal insufficiency skeletal lesions may be found in about half. From the few reports in the literature one would have expected the predominant change to be osteitis fibrosa. This did not prove to be the case, however, since excessive uncalcified bone matrix or osteoid was found in a much larger proportion. Such a pathological picture is similar to that which is seen in osteomalacia or adult rickets. Osteomalacia in this country is thought to be a rare disease in adults, though in older children the presence of excessive osteoid in the absence of changes at the cartilage-shaft junction is probably more prevalent than many realize (9). The occurrence of excessive osteoid tissue indicates that there is a disturbance in calcium and phosphorus metabolism, which, of course, has been recognized as an accompaniment of renal insufficiency for a long time.

Only a few studies similar to ours have been reported in the literature. In 1931, Bergstrand (6) called attention to changes similar to those of osteitis fibrosa in 2 cases of chronic nephritis, one with and one without parathyroid tumors. He concluded that "the histological changes in the skeletal system in osteitis fibrosa generalisata are not characteristic for this disease." A few years later Mach and Rutishauser (7) reported 5 cases of renal insufficiency of varying duration in all of which there was osteoclastic resorption and fibrosis similar to that found in von Recklinghausen's disease. More recently Ginzler and Jaffe (4) have described similar changes in a study based on 12 cases of chronic renal insufficiency in adults. They conclude that "the changes are not due to a "sedondary" or "renal" hyperparathyroidism but are a consequence of the chronic acidosis induced by the renal insufficiency." It is of interest to note that in none of the above publications was there any mention of excessive osteoid. It should also be emphasized that osteoid is not a conspicuous part of primary hyperparathyroidism (10, 11). It is seen in some instances, however, and when present, may indicate that secondary renal damage has occurred with a consequent further alteration in calcium and phosphorus metabolism.

The presence of osteoid alone or in association with the changes of osteitis fibrosa in the adults we have studied is interesting and may help to throw some light on the pathogenesis of the osseous changes in

the more advanced and clinically recognizable cases of "renal rickets" or "renal osteitis fibrosa" in the younger age groups. It is unfortunate

TABLE II

Summary of clinical data and bone changes in reported cases of "renal rickets" or "renal osteitis fibrosa"

AUTHOR	AGE	DURATION CLINICALLY	SERUM		METASTATIC CALCIFICATION	PARATHYROID HYPERPLASIA	BONE LESIONS*
			Ca	P			
			mg. %	mg. %			
Andersen and Schlesinger (12)	5 mos.	4 wks.	8.5–6.4	6.4–11.3	+	+	?
Andersen and Schlesinger (12)	6½ mos.	5 mos.	Low 6.0–8.0	High 9.0–11.0	+	+	Rickets, slight osteitis fibrosa ?
Brockman (13)	13 mos.	7 mos.					Rickets, scurvy ?
Paterson (14)	21 mos.	11 mos.					Inadequate description
Green (15)	3½ yrs.	About 3 yrs.					Rickets, osteitis fibrosa†
Davis and Rossen (16)	4 yrs.	2½ yrs.	7.6	8.0			Inadequate description
Follis and Jackson	4 yrs.	Since birth	3.2?	24.4			Rickets†
Apert (17)	4 yrs.	Since birth?					Inadequate description
Paterson (14)	7½ yrs.	Since birth					Inadequate description
Parsons (18)	10 yrs.		8.2 7.3	14.3 13.7			Probably rickets
Hamperl and Wallis (19)	11½ yrs.	8½ yrs.				"Not enlarged"	Rickets, early osteitis fibrosa
Gall and Bennett (20)	13 yrs.	Since birth?	5.9	17.4			Osteitis fibrosa, "seams of osteoid of variable thickness"
Lathrop (21)	15 yrs.	3 yrs.	5.9 4.6	9.1 9.5		"Normal"	Rickets, osteitis fibrosa†
Parsons (18)	16 yrs.		3.9	16.3			Rickets
Bergstrand (6)	17 yrs.						Osteitis fibrosa
Shelling and Remsen (22)	17 yrs.	3 yrs.	9.6	8.0	+	Marked hyperplasia	Osteitis fibrosa, excessive osteoid in places†
Hubbard and Wentworth (23)	20 yrs.	11 mos.	13.4			"2 enlarged"	Inadequate description
Langmead and Orr (24)	21 yrs.	7 yrs.				"Enlarged"	Rickets and osteitis fibrosa
Albright et al. (3)	45 yrs.	20 yrs.	8.2	9.8	+	+	Osteitis fibrosa

* The lesions are recorded as we have interpreted them from the author's description.
† We have examined these bones personally.

that of these cases there are relatively few in which pathological studies of the bones were made and even in many of these the descriptions are woefully inadequate. However, from a careful study of the re-

ported cases, of several of which material was available in this laboratory, it is apparent that rickets (osteomalacia) and osteitis fibrosa may exist singly or together in a given case (Table II). The age at which the renal insufficiency begins and the degree of renal impairment must play an important role in determining the final pathological picture. The concept of osteoid and the changes of osteitis fibrosa existing singly or together is not a new one since it has been suggested by others (24, 25). Our findings in adults would only tend to strengthen it further.

On the basis of our present knowledge, it would seem unwise to attempt to explain the skeletal changes we have observed. The problem is far too complex. Many variable factors are concerned. The blood serum protein, calcium and phosphorus, the degree of acidosis, the intake and excretion of calcium, the influence of parathyroid hormone normally and under the influence of renal insufficiency, all must be taken into account. Until pointed experiments are performed on animals, we will not know the exact role of each in cases of renal insufficiency such as those we have studied.

When one comes to consider the high incidence of lesions in the glomerulonephritic group, and the relatively low incidence in the cases of vascular nephritis, it is probable that the duration of the disease is the decisive factor; in the latter group, severe renal insufficiency is usually present for a shorter time than in the former even though long standing hypertension and some evidence of renal damage have been present for many years.

In this study we have not made a detailed examination of the parathyroid glands. Such an investigation entails finding and weighing all these organs at autopsy. This has not been performed routinely.

SUMMARY

In a study of routine autopsies in cases of renal insufficiency of various types, histological changes were found in the vertebrae in half. The most prominent finding was the presence of excessive osteoid tissue so that a diagnosis of osteomalacia was justified. In a lesser proportion the changes of osteitis fibrosa were encountered.

Skeletal lesions were found more often in cases of chronic glomerulonephritis or pyelonephritis than of chronic vascular nephritis.

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EXPLANATION OF ILLUSTRATIONS

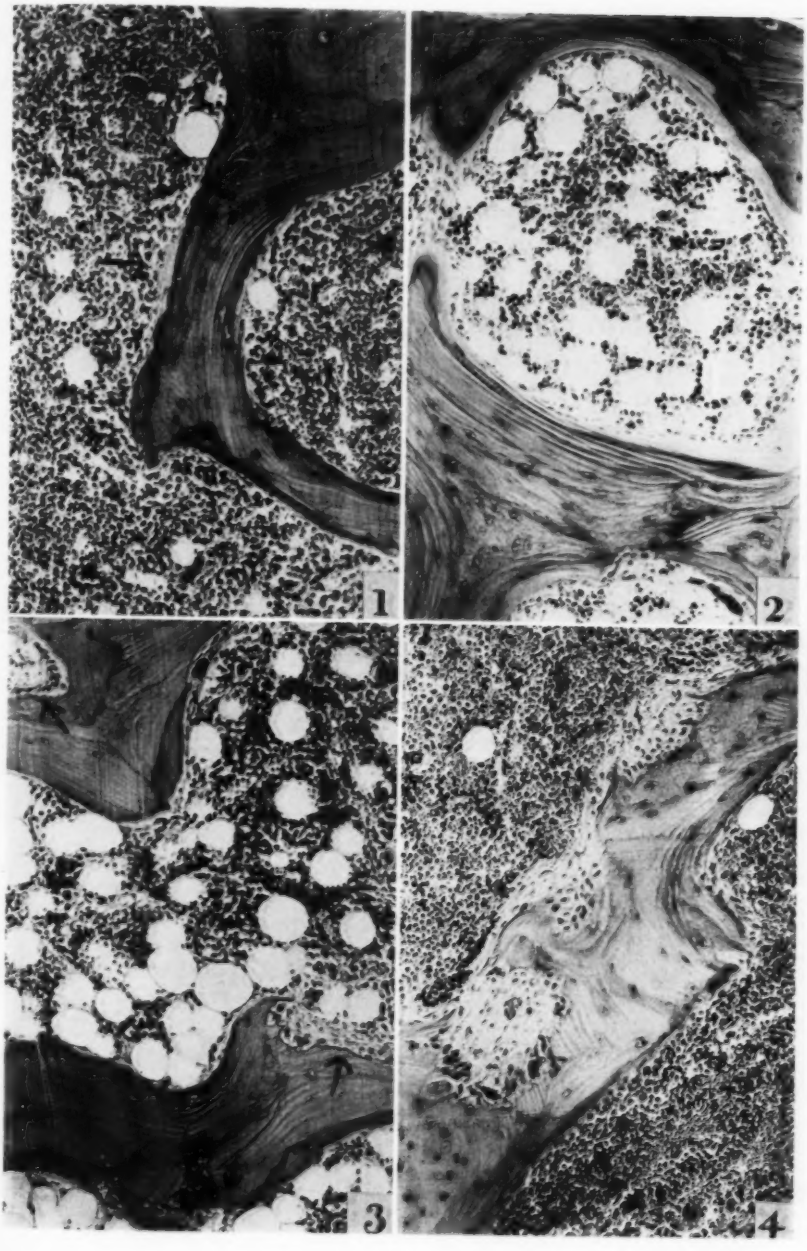
PLATE I

FIG. 1. No. 16812. Chronic vascular nephritis. Shows band of osteoid (arrow) on trabecula. Such borders were present on many of the trabeculae.

FIG. 2. No. 16668. Chronic pyelonephritis. Shows much broader zone of osteoid on 2 trabeculae. Osteitis fibrosa was also present but no lesions are seen in this field.

FIG. 3. No. 16361. Chronic glomerulonephritis. Shows early changes of osteitis fibrosa at arrows. There is excessive osteoid as well.

FIG. 4. No. 16768. Shows more extensive lesion of osteitis fibrosa. No osteoid is present in this field but there was a moderate amount elsewhere.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SALT, CARBOHYDRATE AND WATER APPETITE OF ADRENALECTOMIZED RATS BEFORE AND AFTER TREATMENT WITH DESOXYCORTICOSTERONE PELLETS

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Richter (1) has reported increased appetite of adrenalectomized rats for 3 per cent sodium chloride and distilled water, and a decreased appetite for 40 per cent dextrose solution or solid dextrose (2). Following daily injections of 0.1 cc. of desoxycorticosterone a prompt reversal of these appetites resulted in his rats.

In this work, the rats[1] were kept in separate cages which contained the saltless stock diet (1), and accurately graduated 90 cc. bottles for distilled water, 3 per cent saline and 40 per cent sucrose.[2] Readings were made daily over a period of 70 days. Treatment was given with desoxycorticosterone pellets made with an apparatus previously described (3).

Table I summarizes the results of observations on 13 male 100 day old rats. The average daily sodium chloride intake increased from 1.6 cc. for a 10 day period immediately before adrenalectomy to 8.3 cc. for a 10 day post-operative period. Water intake in our series, however, showed an apparent decrease from 6.7 cc. to 5.9 cc.; sucrose intake decreased from 23.3 cc. to 16.2 cc. Although all these rats showed a definite comparable increased sodium chloride intake after adrenalectomy, the water intake was in no wise similarly increased. All but 2 rats showed decrease in sucrose intake but the average decrease was not nearly as striking as that which occurred in Richter's series (17.3 to 5.8; 13.1 to 2.9) (1) receiving dextrose.

Treatment with 3 pellets of desoxycorticosterone acetate[3] either subcutaneously or intrasplenically (the site does not affect the activity of the hormone (4)) resulted in the average absorption of 0.38 mg. per

[1] Albino rats supplied by the Albino Farms, Red Bank, N. J.

[2] Commercial beet sugar.

[3] Dr. Robert Mautner of Ciba Pharmaceutical Company kindly supplied desoxycorticosterone acetate for these experiments.

day of pellets originally weighing 22.2 to 26.0 mg. Under treatment the average daily sodium chloride intake decreased from 8.3 to 2.4 cc. On the contrary, the water intake increased from 5.9 to 8.5 cc. and the average sucrose intake decreased from 16.2 to 15.1 cc. per day.

TABLE I

Average Daily Intake of 100 Day Old Male Rats Before and After Adrenalectomy and During Treatment with Desoxycorticosterone Pellets

RAT NO.	SODIUM CHLORIDE, 3% SOLUTION			SUCROSE, 40% SOLUTION			DISTILLED WATER		
	10 days before	10 day period after	First 10 days of treatment	10 days before	10 day period after	First 10 days of treatment	10 days before	10 day period after	First 10 days of treatment
Subcutaneous pellets									
5	1.3	11.9	2.2	17	2.5	6.6	14	13.4	20.6
7	1.3	10.8	2.8	16	16.9	21.6	14	4.4	9.2
10	1.0	9.1	1.9	19	16.5	19.8	8.3	8.1	10
11	0.8	6.1	1.8	24.7	14.8	19.4	0.8	7.7	11.3
13	1.9	7.5	1.6	19	15	15.8	1.9	6.9	10.4
Intrasplenic pellets									
3	0.9	7.2	1.9	24.6	17.1	9.7	2.6	2.5	8.6
15	2.3	7.4	2.9	17	22.5	20.2	7.4	5.2	1.8
18	1.0	10.7	3.4	25	15	15	19.7	7.1	6.3
19	1.8	10.7	1.9	29	17.7	16.6	1.6	0.3	0.8
20	3.8	7.9	3.7	43.8	16	6.4	0.3	4	5.9
Without treatment									
4	1.2	7.2		20.7	20.6		5.8	6.3	
8	1.1	6.9		29.1	20.6		3.8	3.9	
9	1.8	5.1		18.6	15.5		6.7	6.9	
Average....	1.6	8.3	2.4	23.3	16.2	15.1	6.7	5.9	8.5

Intake in cc. No allowance made for evaporation.

The sodium chloride appetite of adrenalectomized rats before and after treatment with desoxycorticosterone corresponds to the results obtained by Richter but the water appetite decreased after operation and increased after treatment. There was a moderate decrease in sucrose appetite after adrenalectomy which decreased still further after treatment.

SUMMARY

1. 13 rats in separate cages were given access to 3 per cent sodium chloride solution, distilled water, 40 per cent sucrose solution and salt-less stock diet.

2. Following adrenalectomy the sodium chloride intake increased greatly, but the water intake decreased slightly and the sucrose intake decreased moderately.

3. Absorption of an average of 0.38 mg. per day of desoxycorticosterone from 3 pellets decreased the sodium chloride intake to normal levels, but caused a further decrease in sucrose intake and slight increase in water intake.

4. The markedly increased appetite of adrenalectomized rats of this strain for sodium chloride and response to treatment is comfirmed; a moderate decrease of sucrose appetite following operation is unaffected by treatment; the water intake seemed to follow no significant pattern. The sucrose and water intake curves are not comparable to the results obtained by Richter. There is an apparent difference in the ability of desoxycorticosterone acetate to affect the appetite of adrenalectomized rats for sucrose as compared with dextrose.

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A NOTE ON THE FATE OF INJECTED INSULIN

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The fate of insulin in the body has been the subject for a number of studies. It has been found that following the injection of large doses of this hormone part of it can be recovered in the urine (1) (2), but it has not been established that the limited duration of action of such an injection is entirely the result of its removal by excretion. Kepinow and Ladept-Petit-Dutaillis (3), who employed a portal vein-renal vein anastomosis for liver exclusion in dogs, concluded that the liver inactivates injected insulin or removes it from the circulation. Goadby and Richardson (4) were unable to confirm this finding by means of a complete liver exclusion technique in rabbits. Although the venous drainage of the pancreas is through the liver by way of the portal system, a part of the insulin may, by means of lymphatic drainage, escape passage through the liver.

The present study is an investigation of the possible role of the liver in the inactivation of administered insulin, using a technique previously described for studying the inactivation of estrone and testosterone propionate (5). Under ether anesthesia after a 24 hour fast, laparotomies were performed on albino rats of a Wistar strain, weighing 275 to 325 gm. U-20 insulin (Insulin-Lilly) was injected directly into the liver or spleen by means of a graduated $\frac{1}{4}$ cc. tuberculin syringe. The site of needle entrance was ligated to prevent leakage of the hormone, and the laparotomy incision was closed. The blood sugar curves in these animals were compared with those of animals which were given U-20 insulin subcutaneously immediately after they had undergone laparotomy with injection of distilled water into the liver or spleen. Blood samples from the tail veins were analyzed by the Hagedorn-Jensen blood sugar method (6).

No significant differences in the hypoglycemic curves during a $5\frac{1}{2}$ or 6 hour period could be observed after subcutaneous, intraphepatic or intrasplenic injection of 0.25 units of insulin per 100 gm. of body

weight (figure 1). When the dose was reduced to 0.1 unit per 100 gm. of body weight, the hypoglycemic response to subcutaneous and intrasplenic injection was only slight, and again no significant differences could be noted (figure 2). It needs to be pointed out that the curves

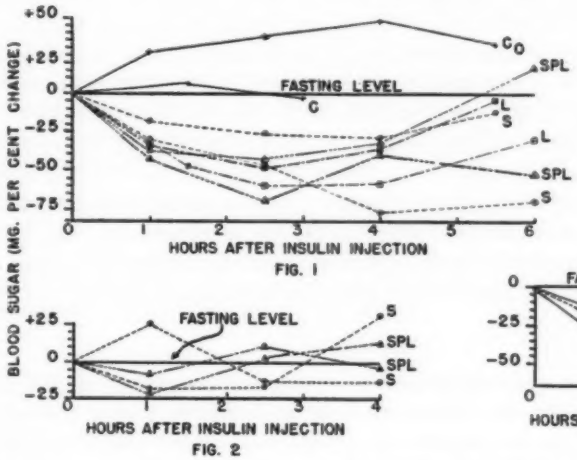

FIG. 1. BLOOD SUGAR CURVES OF RATS INJECTED WITH 0.25 UNITS OF INSULIN PER 100 GM. OF BODY WEIGHT

C = unoperated and uninjected control; C_0 = laparatomized but uninjected control; S = subcutaneous injection, L = intrahapatic injection; SPL = intrasplenic injection.

FIG. 2. BLOOD SUGAR CURVES OF RATS INJECTED WITH 0.10 UNIT OF INSULIN PER 100 GM. OF BODY WEIGHT

FIG. 3. BLOOD SUGAR CURVES OF RATS INJECTED WITH BLOOD CONTAINING 0.25 UNIT OF INSULIN PER 100 GM. BODY WEIGHT OF RECIPIENT

B_C = insulin mixed with blood immediately before injection; B_E = insulin incubated with blood 4 hours at 37°C.

based on the fasting level do not show the total hypoglycemic action of the injected hormone, inasmuch as the hypoglycemic action was superimposed upon a hyperglycemic effect of the ether anesthesia and laparotomy. This hyperglycemic effect was controlled by exposing all of the animals to similar operative treatment.

The possibility that blood itself has the power of inactivating injected insulin during its normal period of action has also been investigated. Two rats were injected intravenously with 5 cc. each of blood which had been incubated for 4 hours at 37°C. with 0.25 units of insulin per 100 gm. of body weight of the recipient. One additional animal received 5 cc. of blood which had been incubated for 4 hours at 37°C., and to which a comparable amount of insulin was added immediately before injection. The hypoglycemic curves in the three rats were similar (figure 3), an indication that blood does not inactivate insulin during this period of incubation. This finding agrees with the results of Goadby and Richardson (4). However, Kohl (7) has reported that a longer period (18 hours) of incubation with blood does partially destroy the hypoglycemic activity of insulin. He has found that the blood of patients with cirrhosis of the liver has less rapid insulin destroying activity than that of patients with no apparent liver damage (8).

SUMMARY

The injection of insulin into the liver, or into the spleen so that it passed through the liver before reaching the peripheral tissues, resulted in the same degree and duration of hypoglycemia as was produced when similar amounts of the hormone were injected subcutaneously. Blood did not inactivate insulin during 4 hours of *in vitro* incubation at 37°C.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Fundamentals of Psychiatry. By EDWARD A. STRECKER. 201 pp. Illus. $3.00. J. B. Lippincott Company, Philadelphia, 1942.

Here is a convenient, small handbook in which the practical minimum of psychiatric understanding has been condensed by a sound practitioner and skillful teacher, in response to the need that "at this time . . . all physicians be versed not only in the routine of medical practice, but also have at least a minimum of understanding of the subdivisions and specialties of medicine . . . particularly of psychiatry."

The outstanding characteristic of this book, in comparison with others, is not elegance of presentation, nor profundity, nor brilliance, but practicality.

There is a chapter on The Psychiatry of the War, which includes the author's admirably succinct suggestions for the management of military neuropsychiatric disabilities, as prepared for the War Department.

J. C. W.

Psychoanalytic Method and Doctrine of Freud. By ROLAND DALBIEZ. Translated by T. F. Lindsay. Two Volumes. 746 pp. $9.00. Longmans, Green and Co., London, 1941.

A critical Frenchman, trained as a philosopher, has carefully analyzed Freud's work and some other psychoanalytic literature (mostly pre-1930). He offers here a two volume presentation and discussion of what he considers the more fundamental and valuable aspects of psychoanalysis. He distinguishes therein a methodology, a psychology and a philosophy. In the main he dismisses the philosophy as amateurish and inconsistent, reflecting the grosser empiricist and positivist errors of Freud's cultural setting, with some individualistic inconsistencies of his own. Dalbiez is particularly critical of Freud's belief in complete determinism.

"His methodolgy is the essential part of Freud's work. His real claim to fame lies in having created a new process of investigation of the unconscious. . . . The discovery of a research technique is more important than any positive result whatever. . . .While methodology is the very essence of psychoanalysis, yet it does not constitute the whole of it, even on the purely scientific plane. . . .The psychological results gained by the method. . .are of very unequal value, and we have tried to discriminate among them, establishing the validity of those which stand close to reality, and eliminating those which derive from the arbitrary introduction of disputable or false postulates."

Dalbiez, like many another, considers the analysis of dreams the greatest of Freud's work. The last sentence in the book is: "Freud's work is the most pro-

found analysis that history has ever known of the less human elements in human nature."

It might be expected that a philosopher's analysis of this "profound analysis" would make rather difficult reading, yet this work is distinguished by clarity, moderation and practical sense. Many may find Dalbiez's presentation easier to take than the original.

J. C. W.

Application of Absorption Spectra to the Study of Vitamins, Hormones and Coenzymes. By R. A. MORTON. 2nd ed. 226 pp. Illus. $6.50. Adam Hilger, Ltd., London, 1942.

The author lays particular emphasis on the importance of absorption spectra in the field of vitamin chemistry and allied compounds. The book includes a sizable amount of data on the spectral analysis of the fat and water soluble vitamins, hormones and chemically related compounds. Numerous figures of absorption curves are presented showing the effect produced on the spectrum by slight alterations in the chemical structure of the compound, as well as the similarity in related compounds. The functional properties and quantitative estimation of the vitamins are discussed briefly, although in certain instances are not brought up to date.

The book should be very helpful to workers in the field of vitamins and hormones, as well as to those who deal with spectroscopy in general.

V. A. N.

Manual of Clinical Chemistry. By MIRIAM REINER. 296 pp. Diagrams. $3.00. Interscience Publishers, New York, 1941.

This manual consists of a compilation of laboratory methods chosen by the author, as the result of years of experience, as being suitable for the chemical analysis of blood, urine and certain other tissues, for many constituents of clinical importance. It is essentially a laboratory guide, with the minimum amount of descriptive or theoretical material, and gives references to the original literature. Because of the simple explicit style in which it is written, this text should prove helpful to many technical workers and students with a limited background in fundamental chemistry. It will, however, fail to help this group in the important respect in which it probably needs help most urgently at the present time, namely, in the adaptation of biochemical methods for use with the photoelectric colorimeter.

M. V. B.

Biology of the Negro. By JULIAN HERMAN LEWIS. 433 pp. $5.00. University of Chicago Press, Chicago, 1942.

This is a carefully chosen summary of such scientific work as is available in the literature dealing with the biology and the pathology of the negro, particularly the similarities and differences that this race displays as compared with the Caucasian.

The first portion of the book deals with the anatomical, biological and physiological characteristics of the negro, and includes some very interesting population

figures that give some statistical measure of the adaptation of the race to the conditions of an alien culture to which it has been forced to adjust in America.

The major portion of the book deals with the negro and his reaction to disease. When possible the author has tried to evaluate the role played by race in the manifestations of disease, distinct from any socio-economic factors that might influence its course. Thus, in so far as the information is available, each disease is studied in the negro, under primitive conditions in Africa, under such conditions of mass grouping as in the African mines, and finally in the negro of the United States.

It is stated in the preface that the book has no thesis to develop or disprove. The material is presented with a certain critical evaluation on the part of the author, but with little bias, and not only makes exceedingly interesting reading, but gives a most valuable bibliography to anyone interested in the biology and the comparative racial aspects of the pathology of the negro.

L. B. E.

Standard Nomenclature of Disease and Standard Nomenclature of Operations. Edited by EDWIN P. JORDON. pp. 1022. $4.00. *American Medical Association*, Chicago, 1942.

This volume consists of the third edition of the *Standard Nomenclature of Disease* and the first edition of the *Standard Nomenclature of Operations*.

Changes from previous editions of the text on disease nomenclature include: 1) About 3500 additions, deletions and corrections to individual diagnostic items, 2) The printing in bold face type of some of the more frequently used terms, 3) Exclusion of numbers corresponding to those in the *International List of Causes of Death*, 4) The addition of a table of eponymic diseases, 5) The omission of *Classified* from the original title. The section on operations is an attempt to set up a standard terminology similar in its arrangement and usefulness to the one on diseases.

Despite the wide acceptance of the Standard Nomenclature by many well known physicians and prominent hospital groups and its sponsorship by the American Medical Association, many students of nosology and the problems of medical nomenclature question the advisability of its widespread use either in the teaching of standard diagnostic terms or in quantitative medicine as a classification of disease entities. Some of the arguments offered are:

a) No standardization of diagnostic entities can be agreed on completely without first defining each term and using it only when it both denotes and connotes precisely a meaning understood by all competent physicians. This would be hard enough for the well defined clinical entities, but when attempted for the poorly defined ones, it becomes almost impossible. Standardization also precludes the use of synonyms and eponyms.

b) The present anatomic and etiological classification is eminently satisfactory for certain diseases, but often becomes quite complicated, particularly in the specialty fields.

c) The numerical coding system is too complicated to be used satisfactorily

either as a diagnostic cross index or as a means for tabulating diseases for statistical purposes. In addition, the time and study necessary to employ the system intelligently is often more than the casual user can afford.

E. L. C.

Immunology. By NOBLE PIERCE SHERWOOD. 2nd ed. 639 pp. Illus. $6.50. C. V. Mosby Company, St. Louis, 1941.

This book is plainly a text book rather than a reference book. The author's interest, ability and experience as a teacher is evident throughout. For the inquisitive student the discussion of many of the topics is inadequate but is supplemented by excellent bibliographies of references at the end of every chapter. The fact that students are stimulated to read these references is in the best tradition of teaching and a compliment to the author.

J. H. B.

BOOKS RECEIVED FOR REVIEW

Civilian Health in Wartime. By FRANCIS R. DIEUAIDE. 328 pp. $2.50. Harvard University Press, Cambridge, Mass., 1942.

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Family Treasures. A Study of the Inheritance of Normal Characteristics in Man. By DAVID D. WHITNEY. 299 pp. Illus. $3.50. Jaques Cattell Press, Lancaster, Pa., 1942.

A Surgeon's Fight to Rebuild Men. An autobiography. By FRED H. ALBEE. 349 pp. Illus. $3.50. E. P. Dutton & Co., New York, 1943.